Measuring and predicting medication adherence using dispensing data and patient beliefs

Harm Geers

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Measuring and predicting medication adherence using dispensing data and patient beliefs

Het meten en voorspellen van therapietrouw bij geneesmiddelen op basis van apotheekaflevergegevens en opvattingen van patiënten

(met een samenvatting in het Nederlands)

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Chapter 1

GENERAL INTRODUCTION

General introduction

Chronic conditions such as cardiovascular or pulmonary disease, diabetes, HIV/AIDS, hypercholesterolemia, osteoporosis and rheumatic disease require long-term pharmacotherapy to prevent further morbidity and mortality. Life-long drug treatment has a huge impact on a person's life, with different problems arising as a disease progresses.

> *Mr G, a 39 year old sales representative is newly diagnosed with hypertension after a routine check-up in order to receive a mortgage for a new house for his recently expanded family. His blood pressure (BP) was approximately 160 over 100 mm Hg on three consecutive occasions and his general practitioner (GP) decides to prescribe hydrochlorothiazide 12.5 mg once daily. He is scheduled for a return visit in two weeks to check his BP. The patient visits his pharmacy to collect the prescription. The pharmacist explains he is being prescribed a diuretic and preferably should take the drug in the morning to prevent frequent nightly bathroom visits. Once at home the patient sits down and reads the package insert. While reading the package insert a lot of questions arise. "Will I receive the loan for my new house, being hypertensive? Will this diuretic cause me racing up and down the toilet when visiting customers? I am in a good physical condition and do not have any symptoms of illness, so how important is reducing my blood pressure? How often do I have to leave work to visit my GP for control of my BP and the pharmacy for refills? How long do I have to take this drug? Will this drug cause erectile dysfunction? What if my BP isn't lowered with this drug? Can I drink a glass of wine in the weekend while on this drug?"*

Questions that arise at the start of drug therapy relate to the change from a 'healthy person' to becoming a 'patient'. This 'healthy person' who is becoming a 'patient' is confronted with a proposal to take a drug for a prolonged period, the length of which is often unknown, and wonders about the necessity and potential side effects. As a patient, he will also struggle with issues like financial consequences of being diagnosed with a chronic condition, the need to change life style and practical considerations such as renewing prescriptions and additional GP monitoring considerations such as frequent doctor appointments. The relevance of these questions may depend on the nature of the disease, is it asymptomatic or symptomatic, severe or less severe?

> *From internet sources, Mr G has learned that 10.9% of all deaths in developed countries are attributable to hypertension [1]. The fact that he has relatives who have suffered myocardial infarctions and CVA's convinces him to start therapy. He is still worried about potential side effects, but decides to give it a try and initiates therapy with hydrochlorothiazide.*

The first decision a newly diagnosed patient has to make is whether he will or will not initiate the prescribed treatment.

> *After two weeks on treatment, G's BP has dropped to 130 / 85 mm Hg and his GP is satisfied. G has not experienced any side effects besides some initial dizziness that passed after a few days. He keeps using his medicine and his initial worries decrease. After nine months his pharmacist asks the patient whether his dosing regimen has changed. G wonders why the pharmacist has this idea. The pharmacist replies that he has not seen the patient for a refill in two months, whereas the pharmacy information system suggests G has run out of stock. G is surprised but realises that he apparently occasionally forgot to take his medication. The pharmacist advices the patient to change from hydrochlorothiazide to chlorthalidone, because the latter drug has a longer duration of action and might compensate an occasionally missed dose (3). After consulting with the GP, the medication is changed to chlorthalidone and for a while G is very conscientious about taking his drug.*

Pharmionics

Typical patient behavior with medicines can be subdivided into three phases, following the definition of pharmionics, introduced by Urquhart in 2005 [2]. Pharmionics is the discipline concerned with quantitative assessment of what patients do with prescription drugs. In pharmionics three phases of ambulatory pharmacotherapy are proposed: acceptance, execution and discontinuation of the drug regimen. Acceptance initiates the process, execution characterises the process and discontinuation terminates the process [2].

Three years later before his yearly summer holiday it is very busy at work, because of the upcoming holiday period. G has little spare time and forgets to pick-up his refill from the pharmacy right before his three-week vacation. During the vacation the patient discovers his drug supply is insufficient to last the entire holiday. Because everything is so nice, G is relaxed and figures this will have no detrimental effect on his BP. Returning home, he has forgotten everything about the antihypertensive drug and does not return to the pharmacy to renew his prescription. After six months G receives a phone call from his pharmacist, asking him if he still uses his diuretic. G suddenly realizes he has terminated his drug therapy. He calls his GP for measurement of his bloodpressure, it has returned to 160 over 100 mm Hg. G is very motivated to restart drug therapy and returns to his pharmacist for a renewal of his prescription.

Adherence is a blanket term covering any type of error in the process. Persistence is the term used to describe the length of time from the first dose to the last dose (discontinuation). Drug taking compliance is the term used to describe the proportion of medicines that is actually taken according to the prescribed dosage regimen. It is important to differentiate adherence, because underlying reasons for (not) initiating therapy may be different from reasons for irregular use or discontinuation of therapy [1, 4, 5]. These decisions are due to both patient factors and drug related factors [6]. Examples for patient related factors are illness perception, a general aversal to use medicines, fear of addiction and/or side effects, forgetfulnes and difficulties in self management such as implementing a routine in drug taking and/or refilling prescriptions [6-10]. The actual occurrence of side effects [4] and complicated dosing regimens [11] are examples of drug related factors.

Measuring adherence

An important reason for differentiation between acceptance, execution (or drug-taking compliance) and discontinuation (or nonperistence) is to clarify the outcome that is presented in studies and reports. Sometimes these outcomes are confusing if presented as 'general patient compliance or adherence'. The following three examples show how difficult it is to interpret such reports of general compliance or adherence. According to the World Health Organization (WHO) only 50% of patients take their medication as prescribed [12]. In a meta-analysis by DiMatteo, the average non adherence rate to medical recommendations is about 25% [13]. Catalan and LeLorier found that only 13%

of the patients initially prescribed a statin were still using the statin after five years of follow-up [14]. These figures on patient compliance are different in outcome and in nature, because they quantify different phenomena in patient compliance. The WHO report may describe both discontinuation and poor taking compliance, while DiMatteo only describes poor taking compliance. Catalan and LeLorier address the magnitude of discontinuation of statin use.

> *After resuming therapy, G again becomes more indifferent towards his drug therapy and now, 20 years later, he has developed diabetes type 2, has increased cholesterol levels and he recently was confronted with chest pain after climbing the stairs. He is referred to a cardiologist and needs an emergency percutaneous transluminal coronary angioplasty (PTCA). After the PTCA, A is discharged from the hospital with an ACE-inhibitor, ß-blocker, statin, metformin, glyburide, acetylsalicylic acid, clopidogrel, and chlorthalidone. G now needs 8 different drugs and while still working as a sales representative, he has difficulties adhering to his drug regimen due to his intensive traveling schedule. As a result he often forgets to take his antidiabetic drug during lunch, resulting in an increased HbA1C. Because of microalbuminuria his ACE-inhibitor dose is increased from once daily to twice daily 20 mg. The increase in therapeutic complexity makes it more difficult to cope with medication taking. Because G forgets some of his drugs more often than others, his supplies go awry and as a result the number of visits to his pharmacy increases.*

A Dutch study on drug taking behavior for major drug categories suggested that 50-70% of patients discontinue drugs early and therefore use drugs ineffectively [15]. The investment loss amounts to hundreds of millions of Euros annually in The Netherlands[15]. During the too short period of actual use, patients may suffer unnecessarily from adverse effects from drugs [15].
Previous research from our group showed that persistence in patients starting with statins decreased to 46% after two years [16]. Even among patients with myocardial infarction and heart failure over 50% discontinued prophylactic therapies such as beta blockers, acetylsalicylic, statins, ACE-inhibitors and spironolactone within 5 years [17-19]. Of patients who started antihypertensive treatment in The Netherlands approximately 22% temporarily discontinued treatment and 39% discontinued treatment permanently [20]. Erkens et al. showed difference in antihypertensive drug persistence with drug class and

gender [21]. In a study investigating long-term antidepressant use only 18.8% of the patients continued to use antidepressants for more than 12 months and 30.2% stopped within 8 weeks after they started [22].

> *G is now 80-years old; the last 15 years of his life were dominated by hospital visits. As a result of his hypertension and escalating diabetes he now has renal failure and needs haemodialysis. This again has increased the number of drugs he has to take, which he now finds unmanageable. Fortunately his pharmacy offers him the possibility to dispense his drugs in an automated dispensing system containing all pills for each particular dosing time. Unfortunately the communication about the frequent dose changes in his phosphate binders and bicarbonate capsules goes by telephone and G forgets most of them and is therefore unable to inform his pharmacy about the dose changes. His (unintentional) non-adherence is unnoticed by both his pharmacy and by his physician.*

Another problem in medication adherence is the complexity of the healthcare system and therapeutic complexity as described for Mr A at the age of 80. Lack of good communication or appointments about how to communicate about dose changes for people with difficulties in medication therapy management is an example in which unintentional nonadherence may be introduced. In the US healthcare system, which is a system with high complexity compared to the Dutch healthcare system, increased therapeutic complexity was associated with increased nonadherence [23].

Identifying patients at risk for nonadherence

It is a challenging idea to be able to identify only those patients that stop taking their medication and those patients that have problems in the execution of their drug regimen before they become nonpersistent or have poor drug-taking compliance.

Interventions to improve adherence to chronic medication therapy are time consuming and therefore costly [24,25]. If employed over an entire population, the intervention would not be very efficient, because there are also patients with good adherence who will not need an intervention. Early identification of patients at risk for becoming nonadherent, would allow employment of a strategy to improve taking compliance and prevention of nonpersistence at an early stage and only in those in need of it. A model that provides this information would be time, and cost saving and increase efficiency in the adherence improvement strategy.

Objectives of the thesis

This thesis has three aims. First, to investigate and describe the way adherence is reported, defined and how reporting of adherence and operational definitions influence adherence estimates. Second, to identify factors associated with nonadherence from both historical dispensing data as well as from prospective data. Third, to investigate whether such factors can be employed in a risk score model that can could be used to predict the risk of becoming nonadherent.

Outline of the thesis

Chapter 2 of this thesis focusus on measurement and reporting issues in adherence. In **Chapter 2.1** a systematic review on different reporting and measurement methods as well as different operational definitions and cutoff values and their influence on reported statin adherence outcomes is presented. **Chapter 2.2** describes measurement methods for nonpersistence and how different exposure outcome combinations influence nonpersistence rates of statins.

Chapter 3 investigates whether historical drug using behavior predicts future nonadherence.
In **Chapter 3.1** a model is presented to identify ambulatory patients at risk for poor taking compliance. This model combines these risk factors in a comprehensive risk score. Sensitivity and specificity of the model are also presented. **Chapter 3.2** presents a model to identify patients at risk for nonpersistence with statins. Different risk factors, like therapeutic complexity and refill consolidation calculated from the PHARMO database and their influence on nonadherence are presented.

Chapter 4 focuses on influence of beliefs about medicines and satisfaction with information on medicines on nonadherence with chronic drug therapy. Moreover the relation between non-reponse and medication adherence is investigated. Data for these studies were collected prospectively. **Chapter 4.1** presents changes in patient's beliefs towards chronic drug therapy during the first months of therapy in new users and relates this with nonpersistence. In **Chapter 4.2** a risk score model that predicts nonpersistence from beliefs about medicines in new chronic drug users is presented. Sensitivity, specificity, positive and negative predictive values are reported. The association between nonpersistence and response or nonresponse as well as the response time are presented in **Chapter 4.3**.

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Chapter 2

Measurement and reporting issues in medication adherence

Different reporting and measurement methods, operational definitions and study characteristics lead to marked variations in adherence outcomes

Submitted for publication

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Abstract

Introduction

To assess whether only poor drug taking compliance, only nonpersistence or both were assessed in published studies of adherence to statin therapy, and whether study outcomes were influenced by the applied methodology and study characteristics.

Methods

A systematic review, meta-analysis and meta-regression analysis of studies with adherence to ambulatory statin therapy as the primary outcome, differentiating between poor drug taking compliance only, nonpersistence only or both poor drug taking compliance and nonpersistence.

Results

The number of different operational definitions and cutoff values found was 26 for drug taking compliance and 18 for nonpersistence. Reported ranges for poor drug taking compliance and nonpersistence varied between 5%-92% and 4%-87% respectively. Studies that differentiate between poor drug taking compliance and nonpersistence, showed lower nonadherence rates (-14% and -19% respectively) compared to studies that do not differentiate. Nonpersistence was lower in self-report (-19%) compared to database studies. Poor drug taking compliance was higher in primary prevention (16%) and in industry sponsored studies (12%). Nonpersistence was higher in new users (18%) and persistence rates increased 3% for each 30-day increase in gap length and decreased with 3% for each 6 months of additional follow-up.

Conclusions

Studies among users of statins show a large variation in reported adherence. Future studies on statin adherence should clearly differentiate between poor drug taking compliance and nonpersistence within the same study and study results should be interpreted with respect to measurement methods, operational definitions, cutoff values and study characteristics.

Introduction

Drug taking behavior, especially the study on what patients do with their prescribed drugs is known in the literature as 'adherence' or 'patient compliance'. It is important to discriminate between different types of adherence, because these can have different causes, lead to different clinical consequences, and require different improvement strategies. Two main forms of suboptimal adherence are nonpersistence, i.e. discontinuation of therapy that is intended to be chronic and poor drug taking compliance, i.e. the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen while still remaining on therapy [1].

Long-term adherence with statin therapy is paramount to reach the beneficial effects on cardiovascular outcomes as reported in large clinical trials [2-4]. A large number of studies have addressed adherence with statins in observational settings to assess use in daily clinical practice. These studies use many different operational definitions of poor adherence, partly dependent on the methods used to measure poor adherence (e.g. prescribing-, dispensing- or claims-records, pill counts, self-report and electronic monitoring). Some studies do not distinguish between poor drug taking compliance and nonpersistence, making it hard to interpret results. In this review we analyzed all published studies on adherence in ambulatory statin users to (1) determine the proportion of studies in which both poor drug taking compliance and nonpersistence were reported and can be separately analyzed and (2) to assess the effects of different measurement methods, operational definitions, cutoff values and study characteristics on reported adherence outcomes.

Methods

Data sources and Searches

Electronic searches in MEDLINE and EMBASE were performed covering 1966 until February 2010. The search strategy was limited to publications in English and varied across databases. For MEDLINE we used the following search strategy:

('Patient Compliance/drug effects' OR '*adherence' OR 'persistence'

OR 'concordance' OR 'compliance') AND ('statin' OR 'statins' OR 'Hydroxymethylglutaryl-CoA Reductase Inhibitors' OR 'lipid lowering drug' OR 'lipid lowering drugs' OR 'simvastatin' OR 'pravastatin' OR 'fluvastatin'or 'atorvastatin' OR 'rosuvastatin' OR 'lovastatin').
In EMBASE we used ('patient compliance'/exp/mj OR 'patient compliance') AND (('hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp/mj OR 'hydroxymethylglutaryl coenzyme a reductase inhibitor') OR ('statins'/exp/mj OR 'statins') OR ('lipid lowering drug'/exp/mj OR 'lipid lowering drug') OR ('simvastatin'/exp/mj OR 'simvastatin') OR ('pravastatin'/exp/mj OR 'pravastatin') OR ('fluvastatin'/exp/mj OR 'fluvastatin') OR ('atorvastatin'/exp/mj OR 'atorvastatin') OR ('rosuvastatin'/exp/mj OR 'rosuvastatin') OR ('lovastatin'/exp/mj OR 'lovastatin')) AND [english]/lim AND [humans]/lim AND [abstracts]/lim.

Study selection and appraisal

One reviewer (HG) screened titles and abstracts to identify articles of potential relevance for this review. Two reviewers (HG, ER) independently assessed the articles for possible inclusion. When reviewers disagreed during study selection, a third reviewer (MB) was consulted, leading to agreement.
All articles were included that (1) evaluated adherence to statins as the primary study outcome, (2) included only ambulatory patients and (3) included only patients of eighteen years or older. Studies that did not discriminate between statins and other lipid lowering drugs (LLD) were excluded. All articles retrieved were cross-referenced in order to identify additional relevant studies.

Data Extraction

Patient and study characteristics as well as adherence measurement and outcomes were extracted from all studies and entered in a predefined data extraction form by one reviewer (HG).

Terminology

The term drug taking compliance was used to specify the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen while still remaining on therapy. The length from initiation to discontinuation of the drug (persistence) is often reported, the term nonpersistence is used throughout this review, because of the focus on the number of patients discontinuing statin therapy. If in this review is stated 'poor

drug taking compliance was higher' or 'nonpersistence was higher' a higher percentage of poor drug taking compliance or a higher percentage of non-persistent patients, is referred to meaning taking compliance or persistence is worse in the referred group.

Reporting of the outcome

Three categories of studies according to reported outcome were identified: (1) only poor drug taking compliance reported, (2) only nonpersistence reported, and (3) both poor drug taking compliance and nonpersistence reported.

Measurement methods

For each study we assessed the measurement method and categorized it into: (1) self-report, (2) pill count, (3) database derived methods and (4) electronic monitoring.
Self-report is generally assessing adherence by asking the patient to what extent he took his medication. This can be done at visits, by telephone or through mailed questionnaires. Pill counts assess taking compliance by asking the patient to bring back his remaining supply of medicine at each visit. From the remaining dosages the average taking compliance of the patient can be assessed. Database derived methods estimate adherence using medication refills as a proxy. Pharmacy records, insurance claims and prescription records are commonly used for this purpose. Electronic monitors are medicine containers equipped with a microchip that registers time and date of every opening.

Operational definitions, cutoff values

Operational definitions provide information on how the raw data are processed to express drug taking compliance and persistence into a numeric value. A cutoff value is the specific numeric value, used by the authors of the study in order to differentiate between poor drug taking compliance and good drug taking compliance or between persistence and nonpersistence. We recorded the different operational definitions and cutoff values used in each included study.

Study / patient characteristics

For each study we extracted the study design, the in- and exclusion criteria, the country from which the data originated, the presence of co-payment the average and maximum follow-up, the indications for statin use (primary (PP) or secondary prevention (SP)), new or prior users, and the funding source (sponsoring from pharmaceutical industry, no involvement from pharmaceutical

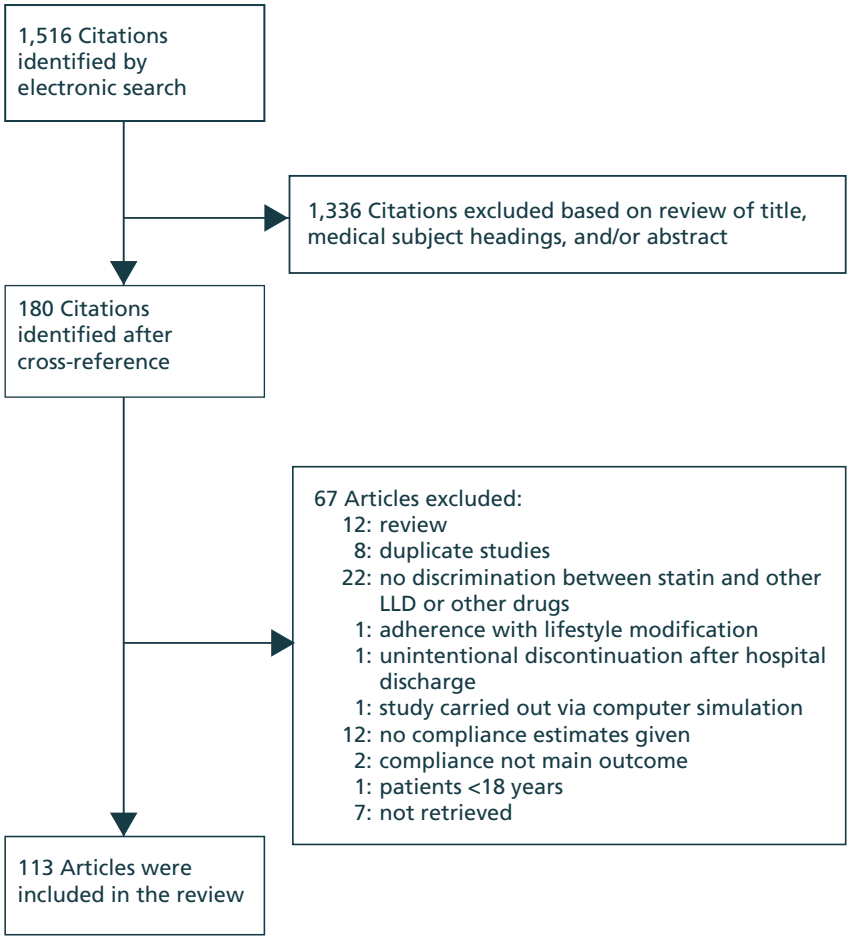
industry or sponsorship unknown). Unrestricted grants from pharmaceutical companies were categorized as sponsorship from pharmaceutical industry.

Data syntheses and analysis

In case of multiple cohorts described in one study, cohorts were analyzed separately. The data were analyzed using R (version 2.13.1, R foundation for statistical computing, Vienna Austria 2011, http://www.R-project.org). Descriptive statistics to present the characteristics of the included studies were used. The "metafor" statistical package to conduct a mixed-effects meta analysis with the inverse variance from the study outcomes of poor drug taking compliance and nonpersistence as the effect estimator, using the restricted maximum likelihood (REML) estimator method was used. If between-study heterogeneity, tested with Cochran's Q-test was significant, we investigated whether the part of the heterogeneity could be explained by the influence of moderators. Different measurement methods, operational definitions, cutoff values and study characteristics as possible moderators to explain heterogeneity were investigated. Only moderators with a p-value<0.05 in the model and compared τ^2 (amount of heterogeneity) for each model to evaluate which model explained most of the heterogeneity were included.

Results

The search strategy in Medline and EMBASE resulted in 1,516 citations, of which after reading title and abstract, 135 were eligible for inclusion. Cross referencing yielded 45 additional articles, resulting in 180 articles for full text examination. We excluded 66 articles for various reasons listed in Figure 1. Included were 113 studies [7-119] that in total included data on 2,979,206 patients.



Abbreviations: LLD Lipid Lowering Drugs

Figure 1: Study Flow

Study / patient characteristics

The mean number of patients per study was 25,910 with a wide range from 40 to 490,024 included patients. The mean of means in age was 61.4 years, 55% were male patients. The total proportion of new statin users was 67% and the total proportion of patients using statins for secondary prevention was 58%.

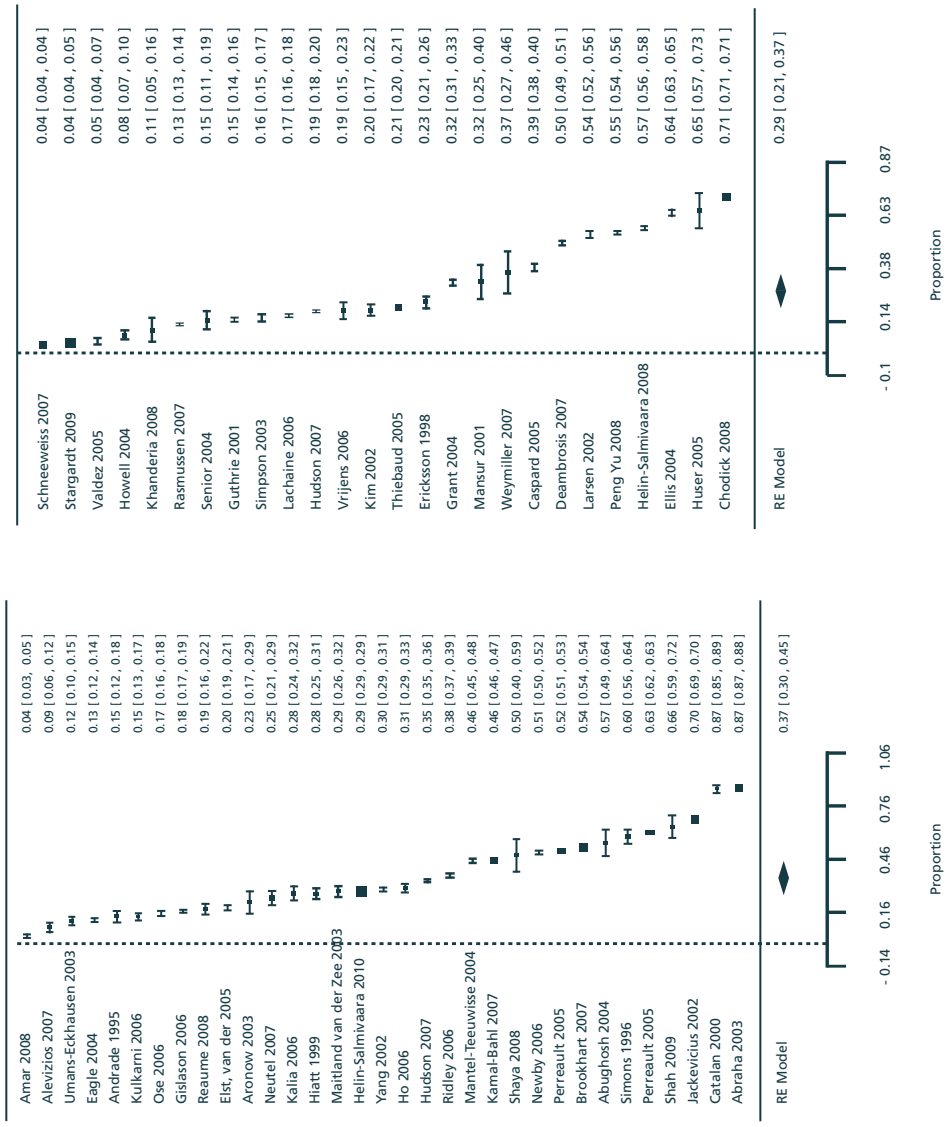


Figure 2.1: Forest plots for nonpersistence in studies reporting only nonpersistence (left), or both drug taking compliance and non persistence (right)

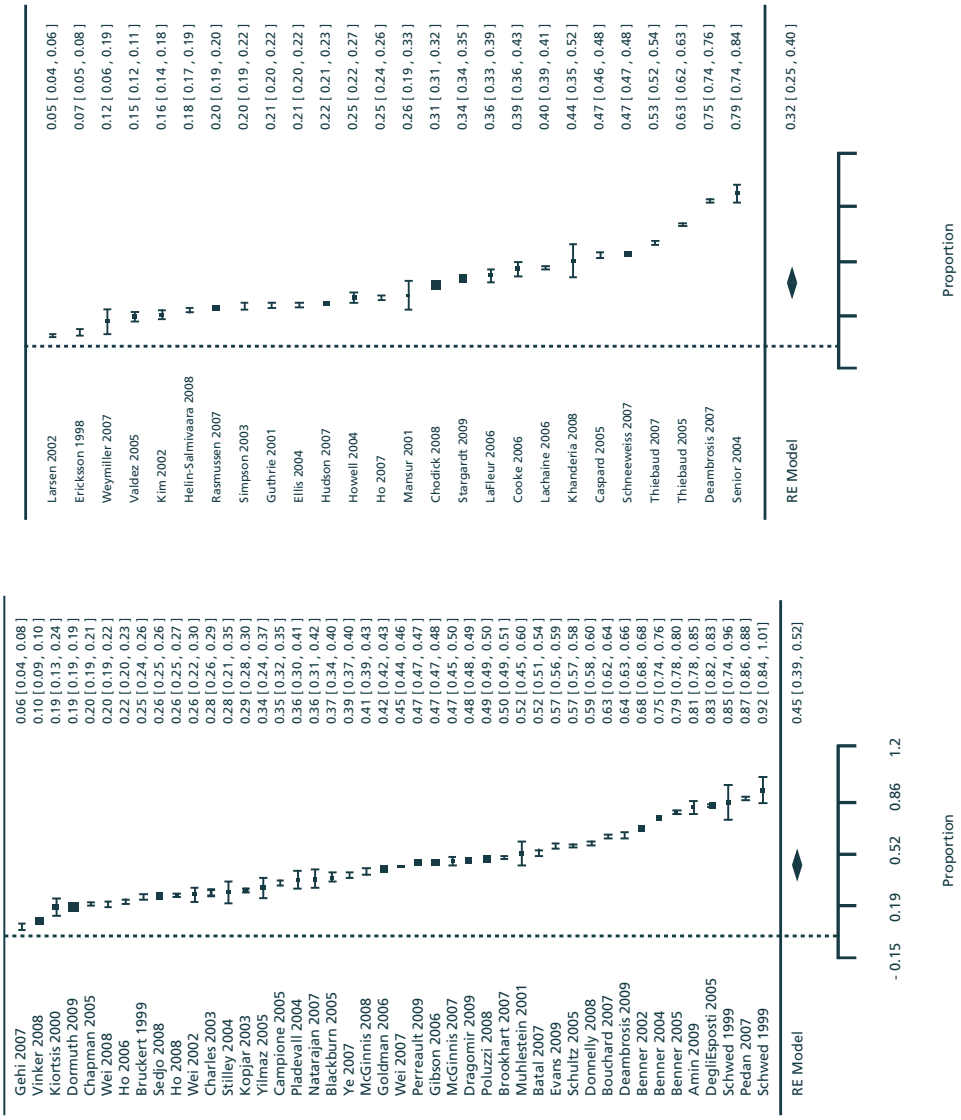


Figure 2.2: Forest plots for poor drug taking compliance in studies reporting only poor drug taking compliance (left), or both drug taking compliance and nonpersistence (right)

The majority of the studies included in this review were retrospective cohort studies (74%), comprising almost 2,800,000 patients (93%). Industry sponsorship was stated in 32 (38%) studies (Table 1).

Discrimination between poor drug taking compliance and nonpersistence

Only 28 studies (27%) assessed both poor drug taking compliance and nonpersistence within the same study cohort [11, 12, 24, 27, 32, 36, 40, 59, 43, 63, 67, 74, 75, 80, 82, 84-86, 90, 96, 99, 100, 109-116]. In studies differentiating between poor drug taking compliance and nonpersistence, absolute differences in pooled estimates were -13% and -8% respectively (Table 2, Figures 2.1 and 2.2), compared to studies without differentiation. A considerable amount of variability in the effect size due to heterogeneity existed ($P<0.0001$, $Q=955,957$). For nonpersistence $Q=766,957$, $P<0.0001$ indicating significant between study heterogeneity.

Measurement methods

Most studies (75%) were carried out in prescriptions or claims databases [7-9, 11, 13-15, 18-32, 35, 37, 41, 42, 46-48, 51, 52, 55, 57, 58, 60-69, 73, 75-78, 80, 81, 83, 84, 86, 88-90, 92-104, 106, 107, 109-120]. Self-report (20%) was the second most common used method [10, 12, 16, 17, 34, 38, 43, 44, 49, 50, 53, 54, 56, 59, 71, 72, 74, 79, 82, 85, 87, 91, 105, 108]. Pill count [33, 40, 45, 50, 70] was used in five and electronic monitoring [36, 37, 50, 70] was used in four studies.

Adherence outcomes and measurement methods

Poor drug taking compliance

In studies using self-report, poor drug taking compliance was 31%, in pill count studies 41%, in database studies 42%. In studies with electronic monitors 4% of dosages were not taken. This means that reported taking compliance was worse in database studies compared to self-report. The 72% poor drug taking compliance reported with electronic monitoring was based on one study (Table 3).

Nonpersistence

Nonpersistence was highest in database studies (40%) compared to self-report (21%). In most studies nonpersistence rates were based on gaps in the medication history (Table 3).

Table 1: Study and patient characteristics

	Study characteristics N=113		Patient characteristics N=2,979,206	
	N (% or range)		N (% or range)	
Number of patients/study			25,910	40 - 490,024
Mean age (years)			61.4	42.2 - 76.4
Female patients (%)			1,334,684	44.8%
Study design				
Retrospective cohort	84	74.3%	2,778,073	93.2%
Prospective cohort	13	11.5%	12,525	0.4%
Cross sectional	4	3.5%	1,184	0.0%
Clinical trial	6	5.3%	10,088	0.3%
Nested case control study	3	2.7%	127,470	4.3%
Other	3	2.7%	49,866	1.7%
Country				
US	55	48.7%	946,659	31.8%
Europe	30	26.5%	900,444	30.2%
Canada	20	17.7%	857,702	28.8%
Other	8	7.1%	274,401	9.2%
Follow-up (months)				
Average	22.5	1-60		
Maximum	36	1-140		
Type of prevention				
Primary prevention			1,287,796	43.2%
Secondary prevention			1,691,410	57.8%
Type of user				
New statin users			1,998,321	67.1%
Prior statin users			980,885	32.9%
Data source				
Database	83	73.5%	2,943,310	98.8%
Hospital	12	10.6%	9,541	0.3%
Clinic	11	9.7%	10,401	0.3%
Other	7	6.2%	15,954	0.5%
Funding source				
Sponsored by industry	32	28.3%	570,975	19.2%
No industry based sponsorship	59	52.2%	2,072,704	69.6%
Not mentioned	22	19.5%	335,527	11.3%

Table 2: Characteristics and outcomes of studies investigating only poor drug taking compliance, only nonpersistence or both poor drug taking compliance and nonpersistence

	Only poor drug taking compliance	Only nonpersistence	Both poor drug taking compliance and nonpersistence	
			Poor drug taking compliance	Nonpersistence
Number of studies	52	33	28	
Number of patients	972,401	1,231,113	775,692	
Self-report	6	12	6	
Pill count	4	0	1	
Database	39	22	20	
Electronic monitoring	3	0	1	
Number of operational definitions	11	3	11	7
Number of cutoff values	9	10	5	10
Outcome range (%)	6-92	4-87	5-79	4-71
Outcome weighted average (%) [95%CI]	45 [38-51]	37 [30-45]	32 [23-40]	29 [21-37]

Abbreviations: CI confidence interval

Operational definitions and cutoff values

An overview of the different operational definitions, number of corresponding cutoff values and measurement methods is presented in Table 4. Most different operational definitions were used in database studies (8 different operational definitions) and most cutoff values (13) were reported in database studies on nonpersistence based on gaps. Ranges in outcomes were wide for all reported outcomes (Table 3).

Table 3: Overview of measurement methods, number of operational definitions, number of cutoff values and outcomes of poor drug taking compliance and nonpersistence

	Poor drug taking compliance				Nonpersistence			
	Number of operational definitions	Number of cutoff values	Pooled estimate [95%CI] (%)	Range (%)	Number of operational definitions	Number of cutoff values	Pooled estimate [95% CI] (%)	Range (%)
Self-report	5	5	31 [18-43]	6-79	1	NA	21 [16-27]	4-51
Pill count	1	3	41 [-10-92]	7-92	NA	NA	NA	NA
Database	9	8	42 [36-47]	5-87	4	17	40 [33-47]	4-87
EM <80%	1	1	72.0	72.0	NA	NA	NA	NA
EM % doses taken	1	NA	4.0	2-13.0	NA	NA	NA	NA

Abbreviations: EM Electronic Monitoring, NA Not Applicable, CI confidence interval

Table 4: Overview of the different operational definitions, number of cutoff values and corresponding measurement methods

Definition	Number of cutoff Values	Measurement method
Drug Taking Compliance		
PDC	4	Database
MPR	3	Database
CMA	1	Database
Fill Frequency	3	Database
ATI	1	Database
CMG	2	Database
DMA	1	Database
MPR and PDC	1	Database
(Pills dispensed-Pills Counted)/Pills dispensed	3	Pill Count
% Doses taken	2	Electronic Monitoring
MARS	1	Self-report
Days with medication	3	Self-report
Self-reported continuous use	1	Self-report
Nonpersistence		
Gaps	12	Database
Self-reported discontinuation	1	Self-report
Prescription refill y/n	2	Database
Not completing study	1	Pill Count
No more data in electronic monitors	1	Electronic Monitoring
MPR	1	Database

Abbreviations: PDC Proportion of Days Covered, MPR medication Possession Ratio, CMA Continuous Measure of Medication Acquisition, CMG Continuous Measure of Medication Gaps, ATI adherence to Therapy Index, DMA Daily Medication Adherence, MARS Medication Adherence Reporting Scale. For the exact definitions we refer to Hess and Steiner [5, 63, 115, 126].

Table 5: Univariate and multivariate effects of moderators after meta-regression analysis of reporting, measurement, patient and study characteristics on poor drug taking compliance and nonpersistence

Variable	Effect of moderator, univariate (%)	95% CI	Effect of moderator, multivariate (%)	95% CI
Poor drug taking compliance				
Measurement=self-report	-11	-25 to 4		
Reported as both poor drug taking compliance and nonpersistence	-13	-23 to -3	-14	-24 to -4
Operational definition	NA	NA		
Cutoff value	NA	NA		
New user	8	-7 to 22		
Primary prevention	16	1 to 32		
Follow-up / month	-0	-1 to 1		
Sponsored by industry	12	0 to 23	13	2 to 24
Copayment	11	-21 to 43		
Continent US	7	-7 to 21		
Nonpersistence				
Measurement=self-report	-19	-30 to -7		
Reported as both poor drug taking compliance and nonpersistence	-8	-19 to 3	-19	-34 to -2
Operational definition	NA	NA		
Cutoff value / 30 days gap	-2	-4 to -0	-3	-5 to -1
New user	18	2 to 34		
Primary prevention	16	-1 to 34		
Follow-up / 6 months	1	0 to 2	2	0 to 3
Sponsored by industry	-11	-24 to 2		
Copayment yes	-3	-23 to 17		
Continent US	-8	-22 to 7		

Abbreviations: CI confidence interval, NA not applicable.
Note that a negative sign of an effect moderator represents better drug taking compliance or persistence.

Effect moderators

Potential effect moderators are reported in Table 5. Significant effect moderators for poor drug taking compliance were self-report (11% better taking compliance), reporting both poor drug taking compliance and nonpersistence (13% better taking compliance), taking statins for PP (drug taking compliance 16% worse), and sponsorship by industry, which was associated with 12% poorer taking compliance. From the multivariable meta-regression analysis, only sponsorship by industry and the reporting of both drug taking compliance and nonpersistence remained significant (Table 5). The estimated amount of residual heterogeneity (τ^2) was 11% lower if the two moderators were included in the model, suggesting that including the two moderators in the model explains 11% of the total amount of heterogeneity (data not shown).

Individual effect moderators for nonpersistence were self-reported nonpersistence, reporting both poor drug taking compliance and nonpersistence, the cutoff value, whether new users were included and follow-up (about 1% more nonpersistence per 6 months of extra follow-up). From the multivariate meta-regression analysis about 32% of the total amount of heterogeneity could be explained by including the reporting of both poor drug taking compliance and nonpersistence, a 30-day gap (3% higher nonpersistence rate for 30 additional gap-days) and follow-up.

Discussion

This review shows considerable variation in adherence outcomes among studies. Two factors that explain this variation in poor drug taking compliance and three for explaining nonpersistence were identified. Most important, studies that differentiate between poor drug taking compliance and nonpersistence, show lower nonadherence rates compared to studies that do not differentiate. Numerous operational definitions and cutoff values are used. The latter results in many different combinations of definitions and cutoff values and may produce large variation in reported outcomes. It was not possible however to demonstrate this using meta-regression analysis, because too many definitions were involved for poor drug taking compliance and nonpersistence. For nonpersistence the large variation in cutoff values was significantly associated with the variation in nonpersistence rates.

Reporting of adherence

The studies reporting only poor drug taking compliance often calculated poor drug taking compliance based on the percentage of days that a patient had medication available. A patient with 79% taking compliance may be regarded as a poor adherer. This assumption may change however if the distribution of days without medication is regarded. Taking medication 79% of the time means not taking medication 21% (or 76 days in one year) of the time. No conclusions about the distribution of these days without medication can be drawn; the days without medication can be subdivided into 4 periods of 19 days or one period of 76 days or any number of periods without medication. If a period of 76 days occurs at the end of the observation period it is more likely that the patient is non-persistent instead of using his medication on an irregular basis. So in studies measuring only drug taking compliance, non-persistent users are likely to be falsely classified as patients with poor drug taking compliance. In this study we observed that reporting only poor drug taking compliance resulted in an increase in poor drug taking compliance of 14% (Table 5). Studies reporting only nonpersistence had an increase in nonpersistence of 19%. The latter may be explained by more strict definitions used in studies that report both poor drug taking compliance and nonpersistence. This also follows from Table 5, since each 30 days increase in gap length is associated with a decrease in nonpersistence of 3%. Therefore, future studies should differentiate between nonpersistence and poor drug taking compliance.

Measurement methods

The studies using self-report, reported better taking compliance and persistence. For self-report, the presence of recall bias and the likelihood that patients give social desirable answers may explain better adherence. [121-123]. Another explanation may be the Hawthorne effect, since patients reporting taking compliance or persistence are aware they are participating in a study, while this is not the case if databases are used [124, 125].

Operational definitions and cutoff values

We identified 26 different operational definitions cutoff value combinations for the reporting of taking compliance. As a result, the variety in outcomes was very large, covering almost the entire percentile range (Tables 3 and 4). The number of operational definition cutoff value combinations was 18 for nonpersistence. The variation in nonpersistence is most likely to be caused by

the large number of different cutoff values rather than the small number of different operational definitions (Table 3, Table 5).

Study / patient characteristics

The studies included in this review have a wide range of inclusion and exclusion criteria that may contribute to selection of patients who are more likely to be adherent. First, the type of user, new users showed higher rates of nonpersistence compared to prior users (+18%, Table 5). New users may experience more side effects than prior users and may therefore be more likely to discontinue treatment. New users are also more likely to become non-persistent, because non-persistent users are already weeded out in studies with prior users. Second, patients who received statins for secondary prevention showed lower nonpersistence rates, although not significant. This may be explained by the increased severity of the patient's condition, which may stimulate the patient to adhere to the drug regimen.

Sponsorship of pharmaceutical companies was related to higher rates of poor drug taking compliance compared to studies with no involvement of pharmaceutical companies. In this review nonpersistence was reported in 13% of the industry-sponsored studies compared to 30% of the non-industry-sponsored studies (data not shown). As reported earlier in this article, studies reporting only poor drug taking compliance overestimate poor drug taking compliance due to misclassification of non-persistent patients. The higher rates of poor drug taking compliance in industry-sponsored studies is explained by the reporting of studies with only poor drug taking compliance. In Table 5 we see that the increase in poor drug taking compliance is largely offset by the decrease in nonpersistence in industry sponsored studies, although the latter was not statistically significant.

Limitations and strengths

A limitation of this review is that we could not include all selected studies, 7 could not be retrieved. We believe this has not influenced the results of this review, since the results are based on the analysis of 113 articles, resulting in a good representation of worldwide statin adherence research.

Strength of this study is that we accounted for the influence several effect moderators may have on each other by using multivariate meta-regression.

Implications

The results from this review have implications for the interpretation of adherence outcomes in general. These implications are important for both scientists in the field of adherence and managed care organizations. Scientists, pharmacists and physicians studying adherence have to differentiate between poor drug taking compliance and nonpersistence. Further, definitions and cutoff values as well as selection of patients need to be defined carefully with a minimum introduction of selection bias and misclassification. Managed care organizations have to know how different means of reporting adherence, measurement methods, operational definitions and cutoff values, as well as patient / study characteristics influence adherence outcomes. Further standardization of operational definitions and cutoff values to assess poor drug taking compliance and nonpersistence in both observational and intervention studies should be stimulated, because this will make comparison of outcomes between two or more studies possible and will increase the precision of economic evaluations of nonadherence.

Conclusions

Studies on adherence in users of statins show a large variation in reported poor drug taking compliance and nonpersistence. Studies should differentiate between nonpersistence and poor drug taking compliance to obtain more reliable and comparable adherence outcomes. Adherence estimations should be interpreted carefully, keeping in mind (1) if the study provides both poor drug taking compliance and nonpersistence outcomes, (2) the method by which drug exposure was measured (3) the operational definition and cutoff value that was used and (4) study / patient characteristics leading to selection bias. Although this review included only ambulatory statin users, we believe that results can be generalized to adherence studies in other drug classes as well.

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Chapter 2.2

Estimates of statin discontinuation are influenced by exposure and outcome definitions

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Abstract

Background

Estimates of statin discontinuation are generally high, but show large variations. Unrecognised supplies from previous prescriptions and the operational definitions of statin discontinuation possibly influence discontinuation rates.

Objective

The aim of this study was to investigate if the outcome, discontinuation, was affected by (1) the operational definition used to calculate statin exposure and (2) the operational definition and different cutoff values used to calculate discontinuation.

Methods

Data for this study were obtained from the PHARMO medical record linkage system in The Netherlands. Participants were patients with a new statin and no statin prescription in the preceding year. The outcome, discontinuation, was defined based on a variable number of days without medication after exposure ('Gaps') or based on the availability of supplies 12 months after the inclusion date ('At one Year'). Exposure to statins was assessed by two methods. Method 'No overlap' accounted for only the supplies of the last prescription to calculate exposure, while method 'Overlap' accounted for all supplies from previous prescriptions. We investigated the effect of four exposure outcome combinations on statin discontinuation estimates.

Results

The exposure outcome combinations including 'Overlap' resulted in a 7% unit lower discontinuation rate. At gap lengths of 90 days and longer no differences between 'No overlap' and 'Overlap' were observed. Shorter minimum gap lengths gave higher discontinuation rates compared to longer minimum gap lengths and ranged from as high as 86% to 21%.

Conclusions

If previous supplies are accounted for in the calculation of exposure to statins, lower discontinuation rates are observed. The influence of previous supplies on discontinuation rates is less pronounced than the influence of gap-lengths. The calculation of exposure does not influence discontinuation if gaps longer than 90 days are used to assess discontinuation.

Introduction

Randomized clinical trials have shown beneficial effects of hydroxymethyglutaryl-co-enzyme A reductase inhibitors or statins on cardiovascular outcome and death. To attain these beneficial effects statins should be taken continuously [1, 2]. In daily clinical practice, however, a substantial number of patients discontinue statin therapy [3]. Discontinuation of statin therapy results in the return of LDL levels to baseline within one month and an increased risk of myocardial infarction or death [4, 5]. Studies investigating discontinuation frequently use dispensing databases, which provide ready available information [6-12]. Steiner et al. provided comprehensive methods to assess discontinuation from databases [12]. Studies on discontinuation of statins report variable discontinuation rates, often based on a minimum gap length. A gap is a period in which theoretically no medication is available to the patient. Variable cut-offs for gap lengths from 15 to 360 days are probably responsible for the variation in discontinuation, ranging from 9% to 79% [13-15]. If a gap is found, patients may still have supplies from previous fillings. If patients stockpile supplies from previous dispensings, it is possible that these stockpiles are used before renewing the prescription. In the latter case the gap is 'filled' with supplies from previous dispensings. Studies on discontinuation of statins generally calculate drug exposure without taking into account previous supplies. Two commonly used definitions are often used to define discontinuation. The first is based on a minimum gap length occurring during follow-up and the second is based on the presence of supplies or not at the end of follow-up [16-19]. Pharmacists or managed care organizations have to know how definitions of exposure and discontinuation of statins may influence discontinuation rates, for three reasons. First, to reliably estimate the number of patients that have discontinued their statin medication, second to identify patients eligible for an intervention or an economical evaluation. Third, it helps them to interpret the results of the literature and put in perspective the outcomes. The aim of this study was to investigate if the outcome, discontinuation was affected by (1) the operational definition used to calculate statin exposure and (2) the operational definition and different cutoff values used to calculate discontinuation.

Methods

Study design

Follow-up study among new statin users.

Setting

Data for this study were obtained from the PHARMO medical record linkage system (PHARMO RLS) in The Netherlands from January 1, 2003 until December 31, 2005. The PHARMO RLS includes drug-dispensing records from community pharmacies of all 950 000 community dwelling inhabitants of 33 medium-sized areas in The Netherlands. The computerized drug-dispensing histories contain data concerning the dispensed drug, dispensing date, dispensed amount and prescribed dose regimen. The clustering of all pharmacies within each city results in drug-dispensing histories that contain more than 95% of all prescriptions dispensed to a particular patient. Drug names are coded according to the Anatomical Therapeutical Chemical (ATC) classification. This study was approved by the PHARMO institutional review board.

Participants

Subjects were included in the study cohort if they were >18 years of age and initiated statin treatment between January 1, 2004 and December 31, 2004. Initiation of a statin was defined as no statin prescriptions and at least one non-statin prescription in the period from January 1, 2003 to December 31, 2003. The duration of the initial statin prescription had to be 15 days or less for this is the maximum amount at the first dispensing in The Netherlands. The maximum amount dispensed in The Netherlands is 90 days' supply but a physician can prescribe any smaller amount as well. All patients had to have a follow-up of at least twelve months, operationalized as at least one prescription 12 months after the initiation of statin treatment. After inclusion, patients were followed until they discontinued statin therapy or until December 31, 2005. A switch between statins (e.g. from pravastatin to atorvastatin) was considered as continuation of statin use.

Exposure/outcome combinations

Two methods were used to calculate the statin discontinuation rate, we refer to these methods as 'Gap' and 'At one year'. We assessed the statin exposure, using methods 'Overlap' and 'No overlap'. The statin discontinuation rates

were calculated based on the four possible combinations: ('Gap', 'Overlap'), ('Gap', 'No overlap'), ('At one year', 'Overlap'), ('At one year', 'No overlap') as presented in Box 1.

Box 1: Definitions of exposure and outcome and combinations of exposure outcome used in study

Definitions

No overlap:
Exposure end date of statin is calculated based on the supplies from the last dispensing.

Overlap:
Exposure end date of statin is calculated based on the combined supplies of all previous dispensings.

Gaps:
Discontinuation of the statin is calculated based on a minimum gap varying from 15 to 180 days in length.

At one year
Discontinuation of the statin is calculated based on the presence/absence of supplies after one year of follow-up.

Combinations of four definitions

Gaps	+	No overlap
Gaps	+	Overlap
At one year	+	No overlap
At one year	+	Overlap

'Gap' and 'At one year'

The study outcome, discontinuation, was assessed using two methods that are commonly used in the literature [16-19]. The 'Gap' method assessed discontinuation based on gaps. Gaps are periods in which no medication is available to the patient. Gaps can be present between two dispensings or after the last registered dispensing of a drug. Many studies have used gaps to assess discontinuation. In the literature, minimum gap lengths between 15 and 180 days are commonly used [13-15]. We used different minimum gap lengths of 15, 30, 45, 60, 90, 120 or 180 days, to define discontinuation. (Box 1)
The 'At one year' method was used for sensitivity analysis and was independent of a minimum gap length. The 'At one year' method assessed the presence of supplies of a statin twelve months after the inclusion date to assess discontinuation.

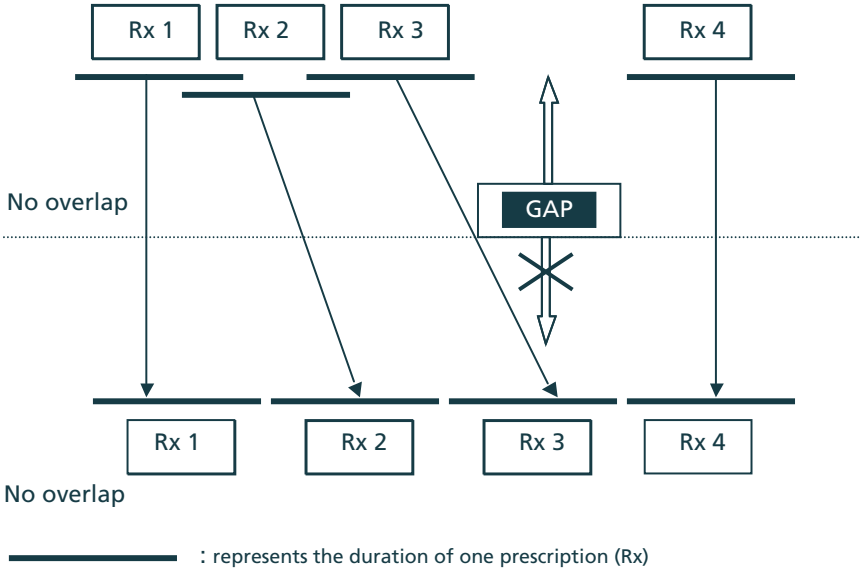

Figure 1: Different methods to assess statin exposure 'No overlap'(upper image): does not account for previous supplies, 'Overlap' (lower image) accounts for previous supplies

'Overlap' and 'No overlap'

The method 'No overlap' accounted for only the supplies of the last prescription to calculate the exposure end date, while method 'Overlap' accounted for all supplies from previous prescriptions (Figure 1, Box 1). For example, if a 60 days' supply was dispensed at t=0, t=40, t=80 and t=200 days, the duration of statin exposure would give two different results, using 'Overlap' and 'No overlap'.

Method 'Overlap' would be calculated as follows: The pickup at t=40 is 20 days too early because prescription pickup at t=0 would have lasted to t=60. The combined pickups at t=0 and t=40 would have lasted to t=120, so the pickup at t=80 is 40 days too early. Combining the pickups at t=0, t=40 and t=80 and accounting for all supplies dispensed results in a total duration of statin exposure of 180 days. The prescription pickup at t=200 is 20 days too late, resulting in a 20-day gap. Method 'No overlap' would let the prescription picked up at t=80 days last until t=140 days, so the duration of statin exposure would be 140 days. The next pickup at t=200 would than be 60 days too late. Using a minimum gap length of thirty days the patient will be classified as having discontinued statin therapy when using method 'No overlap' but as a continuous user with method 'Overlap'.

Dose changes, when registered in the database, were accounted for, because the duration of a prescription was calculated by dividing the number of tablets by the prescribed daily dose for each dispensing.

Statistical methods

Baseline characteristics of the study population and the number of discontinued users were analysed using descriptive statistics. Discontinuation was assessed as a dichotomous value and expressed as the percentage of the total number of patients. Different exposure outcome combinations were compared using the Wilcoxon Signed Rank test, using a two-sided significance level of 5%. Software used was SPSS, version 18.0 (Apache Software Foundation).

Results

We included 6,615 new statin users in our study. The mean age of these patients was 62 years and 52% of the patients were female. Most patients received an initial prescription for simvastatin (36%) or atorvastatin (37%). Almost 50% of these patients concomitantly used beta blockers or calcium channel antagonists and 32% used either an antiplatelet drug or a coumarin at inclusion (data not shown). Follow-up was 365 days.

The upper two curves of Figure 2 represent the exposure outcome combinations ('Gaps', 'No overlap') and ('Gaps', 'Overlap'). At a minimum gap length of 15 days, discontinuation was 86% if 'No overlap' was used to assess exposure. If method 'Overlap' was used, a 7% unit lower discontinuation rate of 79% was observed (P<0.005).

At the minimum gap lengths of 30, 45, 60 and 90 days, discontinuation was also lower in the exposure outcome combination ('Gaps', 'Overlap') (p<0.05). However, at gap lengths ≥90 days, differences between methods 'No overlap' and 'Overlap' are not regarded as clinically meaningful as is illustrated by the merging of the upper two curves in Figure 2.

Discontinuation was high (79-86%) if short minimum gap lengths were used and gradually decreased to 24% at a minimum gap length of 180 days (Figure 2). In the combination ('At one year','Overlap') discontinuation was 21%, compared to 28% for the combination ('At one year', 'No overlap'), as illustrated by the lower two sets of points in Figure 2 (P<0.05).

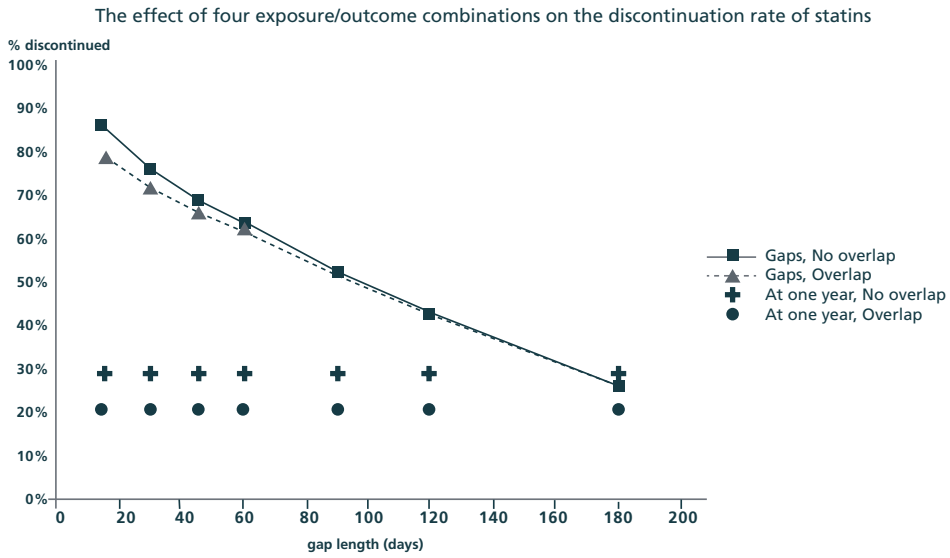

Figure 2: Discontinuation rates of statins, using two methods to calculate the exposure to the statin and two definitions of outcome. Definitions see Box 1

Discussion

This study shows that the method ('Gaps', 'Overlap') revealed lower discontinuation rates at short gap lengths. This implicates that measuring exposure with method 'No overlap' may sometimes overestimate discontinuation. A possible explanation is that short minimum gap lengths may more likely represent nonadherent drug taking behavior instead of discontinuation. If a patient occasionally forgets to take his medication, a short gap appears and he may wrongfully be classified as having discontinued therapy. In method 'Overlap' the previous supplies compensate these short gaps and discontinuation is less likely to be observed. The latter may explain the lower discontinuation rate when using 'overlap'.

At gap lengths ≥90 days, the difference between ('Gaps', 'No overlap') and ('Gaps', 'Overlap') disappears. This is explained by the fact that gaps of 90 days and longer are less likely to be compensated by previous supplies, because this would imply stockpiling of ≥ 90 days, which is unlikely.

Discontinuation rates decreased if the minimum gap length increased. Longer minimum gap lengths to define discontinuation represent more strict definitions. Another possibility is that during the follow-up of one year, it is less likely that observations in which minimum gap lengths are as long as 180 days (half the observation period) are made.

If the absence of statin supplies after one year of follow-up is considered ('At one year', 'No overlap') vs. ('At one year', 'Overlap'), discontinuation is lower if previous supplies are accounted for (i.e. if 'Overlap' is used). The previous supplies that are added to the total duration of the exposure form an explanation for this. If the duration of exposure becomes longer, it is more likely that after the follow-up of one year a patient is still using his statin.

Our findings of a discontinuation rate varying from 21% to 86% correlate with a meta-analysis on predictors to statin nonadherence by Mann et al. who reported discontinuation rates between 13% and 80% [20].

Hudson et al. assessed the influence of different definitions on discontinuation outcomes and found a wide range in discontinuation rates varying from 9% to 94%. In this study a permissible gap, ranging from 1 to 120 days (fixed gap) or 3% to 400% (variable gap) of the duration of the previous prescription was used to define discontinuation. In addition the absence of a filled prescription in the last 60 days of follow-up was used to define discontinuation. Similar to

this study we also found a lower discontinuation rate with the latter method compared to the method based on gaps [21]. Our study differs from the Hudson study in the way we attempted to exactly calculate the grace period. Instead of using a permissible gap we allowed the patient to take all his previous supplies before counting days without medication (gaps), which resulted in lower discontinuation rates at short gap lengths.

Limitations and strengths

McGinnis et al. found that both discontinuation and adherence are overestimated in prescription databases, because as much as 50% of patients classified as being nonadherent, have reasons for discontinuation [22]. Overestimation due to planned discontinuation (i.e. discontinuation with a reason) could not be assessed in our study, but it is likely that results reported in our study are also overestimated due to this phenomenon. However, planned discontinuation is unlikely to have influenced the differences resulting from the applied exposure outcome combinations in this study.
The short follow-up of the study may also have been a limitation to our study. The maximum quantity of dispensed drugs is usually 90 days in The Netherlands, with a maximum of 15 days for the first dispensing. This may have limited the number of dispensings to a maximum of four in some cases. A limited number of dispensings may reveal only limited stockpiling. At longer follow-up stockpiling may become more important. A study by Brookhart et al. observed that 48% restarted statin therapy within one year after a 90-day gap had been exceeded [10]. Some of these restarts may have been due to stockpiling from previous dispensings. The latter may also explain why no differences at longer gap lengths (i.e. ≥90 days) were observed between methods 'No Overlap' and 'Overlap'.

Another limitation is that patients may have been hospitalized or have received medication samples from their physician during follow-up and therefore have been falsely classified as having discontinued statin therapy. In The Netherlands law forbids issuing of medication samples by physicians, making the latter unlikely. We had no records of hospitalization. Another reason for a short gap may be temporarily discontinuation in response to drug-statin interactions that may increase statin blood levels (e.g. a short macrolide antibiotic course). However, these drug interactions are uncommon and when occurring will only result in very short gaps (7 days).

Our study has two strengths; first, we assured new statin use by selecting only patients with a prescription of 15 days and no statin prescription in the previous year. This has limited the number of patients restarting statins after a long drug holiday. Second, we assessed discontinuation in two different ways ('At one year' and 'Gap') to investigate if calculation of statin exposure influenced discontinuation. This sensitivity analysis revealed limited influence of exposure measurement on discontinuation at longer gap lengths. At shorter gaps and with gap-independent methods however, discontinuation rates were lower indicating that different exposure measurements influenced discontinuation.

The findings of this study are relevant with respect to the literature. Discontinuation estimates should be interpreted keeping in mind the operational definition that was used as well as the cutoff values, because these are responsible for a large variation in discontinuation. In the literature many studies use method 'No overlap' or use gap lengths shorter than 90 days [7, 8, 13, 23-31]. Based on our results and based on the results of McGininis et al., it is likely that these studies overestimate discontinuation [22].
Possible clinical implications with respect to our study can be conjectured from the findings of Hughes et al. and Ho et al. suggesting that a 30-day gap without medication may be clinically significant in patients who discontinue statins after a MI. First, because LDL levels rise to baseline again and second, because a positive association with death has been found if statins are discontinued one month after MI [4, 5]. With respect to the results of our study a 5% unit lower difference would be observed in the expected number of patients who would discontinue statin therapy if 'Overlap' was used compared to 'No overlap'.
Future research on discontinuation should account for previous supplies if short gaps are chosen to assess discontinuation. Longer follow-up studies should reveal whether previous supplies influence discontinuation if longer gap lengths are considered because more stockpiling may have occurred, especially if large supplies (e.g. >90 days) are dispensed, during longer follow-up.

Conclusions

Methods to assess discontinuation give variable results and are highly influenced by the operational definition and cutoff values to calculate discontinuation. Discontinuation rates are lower at short gap lengths if previous supplies are accounted for. Although this study focused on statin users, we believe that results can be generalized to other chronic therapies.

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Chapter 3

Prediction of medication adherence from historical dispensing data

Early identification of long-term poor drug taking compliance in ambulatory patients using a multivariate risk score model

Adapted from Ann Pharmacother 2006;40:2277-8

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Abstract

Introduction

Early identification of long-term poor drug taking compliance is of great importance for clinical practice. We investigated the feasibility of early identification of long-term poor drug taking compliance in ambulatory chronic drug users, using a multivariate risk score model.

Methods

A nested case control study was conducted with poor drug taking compliance (continuous measure of medication acquisition (CMA) <0.8) after one year as the main outcome. Included were 2,287 ambulatory patients who started 3,845 new prescribed drugs between July 1997 and June 2002, that were continued for at least one year after the sixth fill (index date). Possible predictors for poor long-term taking compliance were age, gender, chronic disease score, number of prescriptions per year, number of different drugs between inclusion and index date, number of prescribing physicians between inclusion and index date and time between inclusion and index date. All predictors with a p-value <0.05 were included in a multivariate logistic regression analysis to calculate a risk score model that assigned a risk score to each predictor.

Results

After multivariate analysis four significant predictors remained: Age ≤ 60 years (OR 1.4 [95%CI 1.2-2.8]), number of prescriptions per year ≤ 30 (OR 2.1 [95%CI 1.7-2.7]), number of different drugs between inclusion and index date < 20 (OR 1.6 [95%CI 1.1-2.5]) and poor drug taking compliance at the second (OR 2.6 [95%CI 2.1-3.1]), third (OR 3.6 [95%CI 2.9-4.3]) fourth (OR 4.3 [95%CI 3.5-5.3]) or fifth fill (OR 4.5 [95%CI 3.9-5.5]). With the multivariate risk score model identification of poor drug taking compliance increased from 16% to 35%.

Conclusion

Early poor drug taking compliance is an independent predictor of long-term drug taking compliance.

Introduction

In developed countries poor drug taking compliance in patients suffering from chronic diseases is about 50% [1]. For example, in diabetes, hypertension and asthma poor compliance leads to considerable cost increase [1] and in HIV positive patients taking compliance with highly active antiretroviral therapy is a critical determinant of survival [2]. Factors that predict poor drug taking compliance are of great importance, as is the time necessary to identify patients with poor drug taking compliance. If patients at risk for poor drug taking compliance can be identified early and more efficient, interventions to improve medication adherence can be focussed on patients at risk.This will result in higher benefits of drug therapy and lower costs. Pharmacy claims data are commonly used as a source to evaluate medication use including taking compliance to the prescribed drug regimen [3, 4]. Pharmacy records represent a better measure of taking compliance than self-report [5]. Pharmacists are the key administrators of the pharmacy records and therefore have the best position to overview drug records and signal poor drug taking compliance and may also play an important role in improving drug taking compliance [6]. Problems resulting from poor drug taking compliance may already be present at the moment it is detected, because medication may have been used for a considerable period of time [2, 7, 8]. We therefore investigated if early identification of long-term poor drug taking compliance for chronic medication is possible, using pharmacy dispensing records.

Methods

Setting

The study was conducted using the prescription dispensing database of a Dutch community pharmacy serving approximately 14,000 patients. The dispensing history of these patients is virtually complete, since the pharmacy database is linked to all general practitioners in the city, meaning that prescriptions from general practitioners are sent to the pharmacy real time through a data communications network. A prescription record contains the patient number, drug prescribed, date of the prescription, amount of drug dispensed and the

prescribed regimen for every fill. Prescriptions from the regional hospital are faxed to the pharmacy for every registered patient of the pharmacy. The pharmacy is the sole pharmacy in the city. The database has prescription data available from the first of January 1997 adding up to a total of 807,525 prescriptions and 18,705 registered patients. The number of registered patients exceeds the number of patients served by the pharmacy because patients move without notification or die and some registered patients do not use medication.

Study population

For the present study, we included all ambulatory patients starting with a new prescription drug that was filled five times and continued for at least a year after the sixth fill, starting the first of July 1997 until the seventeenth of June 2002. A prescription was defined as new, if the drug was not used in the previous six months before inclusion, changes from the branded drug to a generic drug were not considered as the start of a new prescription. In The Netherlands patients receive their first prescription for 14 days as ordered by law. Repeat prescriptions can be dispensed for a maximum of 90 days, but smaller intervals are allowed. Average interval between two prescriptions is about 60 days.

Study design

Within the cohort of long-term new drug users, a nested case control study was performed. Drug taking compliance was defined as the cumulative days of supply obtained, divided by the total number of days in the interval in which it was obtained (CMA) [4]. Patients were defined as cases if the CMA was ≤ 0.8 during the one-year period following the sixth fill, the sixth fill was defined as the index date. Controls were patients in which the CMA over the one-year period following the index date was > 0.8. Investigated as predictors of interest were the CMA ≤0.8 up to the second, third, fourth and fifth fill, number of different drugs used, time between inclusion and the index date, total number of prescriptions, age, sex, chronic disease score (CDS) and the number of different prescribing physicians [9]. The total number of different drugs used between the first fill and the index date was subdivided into less than twenty or more than twenty different drugs used, including drugs that might be used for short periods of time. The number of prescriptions was determined over a one-year period from the inclusion date as was the CDS. Subjects were subdivided as receiving thirty prescriptions or less and a CDS score of four or less. The number of different prescribing physicians between the first fill and the index

date was divided into three or less prescribing physicians or more. There were no other exclusion criteria. It was possible that one patient was included more than once if he started more than one new drug during the inclusion period.

Data Analysis

Characteristics of the study population at the index date were analysed using the one sample t-test with a 95% confidence limit. Strength of association with poor drug taking compliance was expressed as odds ratios for all potential prognostic determinants. All factors with a p-value < 0.05 in the univariate analysis were included in a multivariable logistic regression analysis. For each refill the reliability (goodness of fit) was quantified using the Hosmer and Lemeshow test [10]. The predicted values from the logistic regression model were used to construct receiver operating characteristic (ROC) curves and to calculate the area under the ROC curves (AUC). The AUC is a suitable parameter to summarize discriminative or predictive value and can range from 0.5 (no discrimination) to 1.0 (perfect discrimination) [11]. The adjusted regression coefficients of the model were multiplied by a factor 10 and rounded to the nearest integer to obtain an individual risk score for each predictor. The total risk score was calculated for each case by assigning points for each predictor present and adding these points. Analogue methods were performed for the fourth and fifth fill. The total scores were subdivided and sensitivity and specificity of the risk score was calculated for the different cut-off values. Software used was SPSS for Windows, version 12.0.1 (Apache Software Foundation). All p-values are two sided.

Results

A total of 2,287 patients and 3,845 newly started drug treatments were included, resulting in an average of 1.7 drugs per patient, characteristics of the population and of the newly started drug treatments at the index date are depicted in Table 1 and Table 2. Overall poor drug taking compliance was 16% one year after the index date. Table 3 shows the crude odds ratios for each predictor of the univariate model. Strongest predictors of poor drug taking compliance were age ≤ 60 (OR 2.8 [95%CI 2.3-3.4]), receiving the first five fills in 4 months

(OR 1.4 [95%CI 1.0-2.0]), number of prescriptions ≤ 30 in one year after inclusion (2.4 [95%CI 1.7-3.4]), less than 20 drugs used between inclusion and the index date (OR 1.2 [95%CI 0.9-1.4]) and a CMA ≤0.8 at the second (OR 2.8 [95%CI 2.3-3.4]), third (OR 3.7 [95%CI 3.1-5.4]) fourth (OR 4.4 [95%CI 3.7-5.4]) or fifth fill (OR 4.6 [95%CI 3.8-5.5]).

Inclusion of all predictors with a p-value <0.05 in the multivariate model resulted in four independent predictors (Table 4), early poor drug taking compliance (i.e CMA ≤0.8 at the second (OR 2.6 [95%CI 2.1-3.1]), third (OR 3.6 [95%CI 2.9-4.3]), fourth (OR 4.3 [95%CI 3.5-5.3]) or fifth fill (OR 4.5 [95%CI 3.7-5.5]), age ≤ 60 (OR 1.4 [95%CI 1.1-1.9]), 30 prescriptions or less one year after inclusion (OR 2.1 [95%CI 1.7-2.7]) and less than 20 drugs used between inclusion and the index date (OR 1.4 [95%CI 1.1-1.9]). The results for the Hosmer-Lemeshow goodness of fit for taking compliance at the second, third, fourth and fifth fill were respectively 0.417, 0.887, 0.584 and 0.504 and the area under the receiver operating characteristic curve for the reduced model respectively 0.676 [95%CI 0.65-0.70], 0.699 [95%CI 0.68-0.72], 0.714 [95%CI 0.69-0.74] and 0.718 [95%CI 0.70-0.75]. Poor drug taking compliance is predicted correctly in 65-70% of the cases according to the model. The fit of all models was good with the best fit for taking compliance at the third fill (Hosmer-Lemeshow statistic: 0.887). We transformed the model for the third fill in a scoring rule, the scores are depicted in Table 4, CMA at third fill ≤0.8 +13, age ≤ 60 +3, less than 20 different different drugs used between inclusion and the index date +4, 30 fills ore less in one year +8. Such a scoring rule can be considered as one overall measure for patients at risk for long-term poor drug taking compliance. Table 4 shows the incidence of poor drug taking compliance among patients across different score categories at the third fill. From Table 5 one can directly obtain the observed poor drug taking compliance per score category by reading horizontally. Similarly the positive and negative predictive values for various cut-off points can be calculated: the positive predictive value for a score ≥ 17 is 215/651=33%, while the negative predictive value of a score <17 is 2803/3194=88% for taking compliance at the third fill ≤ 0.8. Reading Table 5 vertically provides estimates of the sensitivity and specificity at different thresholds.

Table 1: Baseline characteristics

Patient characteristics	Value (%) [95% CI] N=2287
Male gender	955 (41.7%)
Mean Age	67.1 [66.4-67.8]
Number of patients	2287
Average number of included drug classes per patient	1.7
Time between inclusion and index date (months)	9.3 [9.1-9.5]
Number of drugs used between inclusion and index date	11.7 [11.4-12.0]
Median number of prescriptions between inclusion and one year	61

Table 2: Top ten of included drug classes

Drug class	ATC	N	%
Antithrombotics	B01	369	9.6
ACE and AT2 receptor antagonists	C09	314	8.2
Beta blockers	C07	312	8.1
Diuretics	C03	281	7.3
Antacids	A02	249	6.5
Lipid lowering drugs	C10	241	6.3
Antidepressants	N06	237	6.2
Antipsychotics and anxiolytics	N05	231	6.0
Antidiabetics	A10	222	5.8
Calcium channel blockers	C08	171	4.5

Abbreviations: ACE Angiotensin Converting Enzyme, AT2 Angiotensin 2, ATC Anatomical Therapeutical Chemical code.

Table 3: crude association and adjusted odds ratios of potential prognostic determinants of poor compliance one year after the index date

Predictors of poor compliance	N (%)	Poor drug taking compliance[$] N (%)	Crude OR [95% CI]	Adjusted[*] OR [95% CI]
Overall	**3,845**	**606**		
Age ≤ 60 yrs	1,033	213 (21)	2.8 [2.3-3.4]	1.4 [1.2-1.8]
Male gender	1,630	247 (15)	1.0 [0.9-1.2]	NS
Number of fills ≤ 30 between inclusion and one year	1,177	277 (24)	2.4 [1.7-3.4]	2.1 [1.7-2.7]
Number of different drugs < 20 between inclusion and index date	625	103 (16)	1.1 [0.9-1.4]	1.4 [1.1-1.9]
Chronic Disease Score between inclusion and one year ≤ 4	2,627	329 (12)	1.1 [1.1-1.2]	1.0 [0.8-1.3]
Number of prescribing physicians between inclusion and index date ≤ 3	2,413	403 (17)	1.2 [1.0-1.5]	1.2 [0.9-1.5]
CMA ≤0.8				
At second fill	848	238 (28)	2.8 [2.3-2.4]	2.6 [2.1-3.1]
At third fill	822	265 (32)	3.7 [3.1-5.4]	3.6 [2.9-4.3]
At fourth fill	816	283 (35)	4.4 [3.7-5.4]	4.3 [3.5-5.3]
At fifth fill	817	287 (35)	4.6 [3.8-5.5]	5.4 [3.7-5.5]
Time between inclusion and index date				
< 4 months	301	39 (13)	1.4 [1.0-1.8]	NS
= 4 months	474	39 (8)	1.5 [1.0-2.0]	1.6 [1.0-2.6]
>4 months	530	73 (14)	0.95 [0.7-1.2]	NS

Abbreviations: OR odds ratio, CI Confidence Interval

* Odds Ratio was adjusted for number of prescriptions ≤ 30 in one year, number of drugs < 20 between inclusion and index date and age ≤ 60 years. NS means that investigated parameter was not significant in primary analysis and were therefore not investigated in the multivariable logistic regression analysis.

$ Calculated one year after the sixth fill.

Table 4: Regression coefficient and score of each predictor included at the third fill

Predictor	Regression coefficient	Risk score
Refill compliance at the third fill ≤ 0.8	1.29	13
Number of fills ≤ 30 one year from inclusion	0.82	8
Number of different drugs < 20 between inclusion and index date	0.38	4
Age ≤ 60	0.33	3

The risk score per predictor is obtained by multiplying the regression coefficient by ten, rounded to the nearest integer.

Table 5: Performance of the multivariate model at the third fill

Risk score at third fill	Total N=3845	Incidence of poor compliance (%) N=606		Sensitivity (%)	Specificity (%)
>0	1741	145	(8)	100	0
>5	387	36	(9)	76	51
>11	1066	210	(20)	70	61
>17	373	98	(26)	35	87
>23	278	117	(42)	24	95

Discussion

The multivariate model presented in this study improves efficiency in identifying long-term poor compliers from 16% to 35% by using age ≤ 60 years, drug taking compliance at an early moment, number of prescriptions per year ≤ 30 and less than 20 drugs between inclusion and index date as independent predictors of poor long-term drug taking compliance.

We found that age ≤ 60 years was an independent predictor of poor drug taking compliance, this is consistent with findings from Schechtman who found an increase in refill adherence of 1.8 % per decade of increased age with a

plateau at 65 years [12]. An increased mean adherence of 0.76 % per additional drug prescribed was also found, again consistent with findings presented in this study [12]. Shanlansky and Levy found that less medication and less prescription drugs per day were associated with poorer drug taking compliance [13]. These findings are comparable to our findings, since less medication per day suggest less different drugs and prescriptions per year, predictors we found to be risk factors for poor drug taking compliance. We are unaware of any studies that investigated short-term taking compliance as a risk factor for long-term compliance.

Overall poor drug taking compliance was low in our study (606/3845=16%), compared with other reported poor adherence values, which are as high as 50% [1]. However, the World Health Organization report does not discriminate between nonpersistence and drug taking compliance, which are two different measures. We found a lower adherence percentage, because we only included cases that were persistent for more than one year. Van Wijk et al. found that persistence with new users of antihypertensive drugs varied between 57-81% for different number of days between two prescriptions (varying from 30-365 days) and between 57-69% for 1-4 times the duration of the last prescription between two prescriptions [14]. This suggests that high drop out rates occur early in treatment. Since our study lasted at least 360 days plus 9.3 months inclusion time we included only persistent subjects.

The ease in which the described predictors are acquired and used in a risk score model, makes it an attractive tool to identify patients at risk for long-term poor drug taking compliance. This can be automated and used in pharmacy practice. For example, a person of 59 who uses a diuretic and an ACE inhibitor with a taking compliance at the third visit of 0.75 and with 8 fills per year (every 90 days for the diuretic and the ACE inhibitor), receives a score of 3+4+8+13=28 (Table 4) and has a high risk on poor drug taking compliance. Different values can be chosen, depending on drug or co-morbidity as threshold for intervention by a pharmacist. Given the individual score of each predictor, taking compliance (13 points) and 30 fills or less (8 points) seem to be the strongest predictors for poor drug taking compliance. If registered fills in one year are as low as 30 or less, it is probable that these patients have a relatively low health care consumption pattern. It is therefore likely that these patients feel relatively healthy and are unaware of the need to comply with the drug regimen as prescribed. Patients with an age ≤ 60 years may present a group of healthy patients (working population) and may therefore be less frequent health

care consumers and may not feel the need to comply with the prescribed drug regimen.
It is important to improve our ability to identify patients who will and will not be adherent and improve the efficiency of interventions aimed at improving adherence [15]. An intervention strategy on 1000 patients identical to our study, without using the predictive model could at most prevent 160 cases to turn into poor compliers. Using the predictive model would have identified 169 patients at risk and could at most prevent 59 cases of becoming poor adherers. In terms of 'numbers needed to screen (NNS)', we would have to screen 5.2 (1/(0.35-0.16)) patients with our model to identify one patient with poor drug taking compliance. Thus our model improves efficiency in identifying cases at risk for long-term poor drug taking compliance. It is unknown if the multivariate model is generalizable to the entire population of The Netherlands or populations elsewhere.

Conclusions

This study shows four easily obtained factors that predict long-term poor drug taking compliance that can be automated in a pharmacy practice. These factors are taking compliance at the third fill, age ≤ 60 and 30 fills or less one year after inclusion and less than 20 different drugs used between inclusion and the index date. Although not perfect, CMA measured at the third fifth fill ≤0.8 seems to be an independent predictor for poor long-term drug taking compliance, improving efficiency in identifying poor drug CMA from 16% to 35% of the cases. Early identification of poor drug taking compliance is possible using the multivariate model presented in this study, hence interventions to improve drug taking compliance can be done earlier.

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Influence of therapeutic complexity on medication adherence in The Netherlands

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Abstract

Background

A large US database study found that therapeutic complexity was associated with poor medication adherence. The aim of this study was to investigate whether therapeutic complexity was also associated with poor medication adherence in The Netherlands.

Methods

Data for this study were obtained from the PHARMO medical record linkage system (PHARMO RLS) in The Netherlands. Outcomes were nonpersistence (defined as having at least a 60-day gap in dispensing) and poor drug taking compliance (Continuous Measure of Medication Acquisition (CMA) below 80%). Participants were patients with a new statin prescription who were followed for at least 12 months or until they became nonpersistent with statin therapy.

Results

Of the 6,614 incident statin users, 63% discontinued within one year and 5% had poor drug taking compliance. The number of visits, number of fills, number of single dispensings, number of prescribing physicians and total number of switches within each drug class were all significantly associated with nonpersistence. For poor drug-taking compliance only the number of single dispensings was significantly associated. However, for all variables the odds ratios approached 1.

Conclusion

This study showed that although therapeutic complexity is associated with medication adherence, the predictive value of individual variables is low.

Introduction

Several randomized clinical trials have shown that statin treatment reduces cardiovascular morbidity and mortality in patients with increased lipid levels, if taken for a sufficient long period [1-3]. However, population based studies on statin use show that a high proportion of patients using statins both for primary and secondary prevention, prematurely discontinue statin therapy or have poor drug taking compliance [4]. Nonpersistence can be defined as a gap in therapy [5] and generally occurs early after initiation of therapy, with most patients discontinuing treatment in the first six months [6, 7]. Poor drug taking compliance is also associated with increased risk of morbidity and mortality [8]. So nonpersistence and poor drug taking compliance of statins both lead to preventable cardiovascular morbidity and mortality. Pharmacy records are a reliable source for estimating nonpersistence and poor drug taking compliance rates and are commonly used to evaluate medication use [9, 10]. The consequences of nonpersistence and poor drug taking compliance are important from both a cost [11] and clinical perspective. Timely identification of patients at risk for nonpersistence or poor drug taking compliance of statins may help to improve adherence to pharmacotherapy and thereby prevent subsequent cardiovascular morbidity and mortality. Choudhry et al. found in a US study that therapeutic complexity was associated with an 8% increased rate of poor drug taking compliance. Choudry made several recommendations to improve drug-taking compliance, such as the creation of a 'pharmacy home' (i.e. a single pharmacy were patients fill all their medication) and less complexity in prescribing and dispensing [12]. These recommendations are virtually all implemented in The Netherlands. We therefore investigated whether therapeutic complexity in The Netherlands was associated with medication adherence.

Methods

Study design

A nested case-control study in a cohort of new statin users.

Setting

Data for this study were obtained from the PHARMO Record Linkage System (PHARMO RLS) in The Netherlands from January 1, 2003 until December 31, 2005. The PHARMO RLS includes drug-dispensing records from community pharmacies of all 950,000 community dwelling inhabitants of 33 medium-sized areas in The Netherlands. The computerized drug-dispensing histories contain data concerning the dispensed drug, type of prescriber, dispensing date, dispensed amount and prescribed dose regimen. The clustering of all pharmacies within each area results in drug-dispensing histories that contain more than 95% of all prescriptions dispensed to a particular patient. Drug names are coded according to the Anatomical Therapeutical Chemical (ATC) classification.

Participants

Subjects were included in the study cohort if they: (1) were 18 years of age and (2) initiated statin treatment between January 1, 2004 and December 31, 2004. Initiation of a statin was defined as having no statin prescriptions and at least one non-statin prescription in the 12 months before the first statin prescription. The duration of the initial statin prescription had to be equal to or less than 15 days, for this is the maximum duration of a first dispensing in The Netherlands. All patients had to have a follow-up of at least twelve months, operationalized as at least one prescription for any medication after 12 months following the initiation of statin treatment.

Follow-up and study outcome

Patients were followed for 12 months after inclusion, or until they became nonpersistent with statin therapy, whichever occurred first. Patients were considered nonpersistent to statin therapy if no statin was available for at least 60 days between two consecutive prescriptions [13]. Poor drug taking compliance was calculated using the Continuous Measure of Medication Acquisition (CMA) with a cutoff value of 80% [9]. Switching between statins was considered as continuation of therapy.

Covariates

As a proxy for therapeutic complexity, the number of pharmacy visits, total number of dispensings, long-term medication classes, single dispensings (e.g. antibiotic course), dose changes within each drug class, prescribing physicians and total switches within each drug class were calculated 12 months before

statin initiation. The operationalization of the covariates is presented in Table 1. We further calculated refill consolidation according to Choudhry et al. [12]. In short, refill consolidation=1-(number of visits/number of medications filled) with higher values representing more different drugs dispensed per visit, hence less stops at the pharmacy.

Table 1: Operationalization of research variables

Variable	Operationalization
Number of visits	Total number of visits, defined as different dates in the database (e.g. April 13, 2005 and April 19, 2005 equals two visits)
Number of fills	All fills of any drug registered in the pharmacy records
Number of chronic medication classes	First 5 positions of the ATC code fixed. Short term use drugs were included (e.g. antibiotics)
Number of single dispensings	This equals the total number of dispensings that were dispensed only once in the 12 months before initiation (e.g. antibiotic course)
Refill consolidation	1-(number of visits/number of medications filled)
Number of changes within drug class	Within each drug class (first 5 positions of ATC fixed) a change in positions 6 and 7 equaled one change (e.g. C10AA01->C10AA04)
Number of prescribing physicians	Difference in specialism (e.g. GP, Neurologist and Cardiologist equals 3 different prescribing physicians)
Number of dose changes	Any change in frequency or amount of tablets equaled one change (e.g. twice a day->once a day->twice a day equals two changes)

Statistical methods

The association with nonpersistence and poor drug taking compliance for all variables was investigated using binary logistic regression. Odds ratios were calculated for all potential prognostic determinants. All factors with a p-value < 0.10 in the univariate analysis were included in a multivariable logistic regression analysis to construct a predictive model. After each run, using the

'enter' method, the variable with the lowest non-significant association was eliminated until all variables in the model had a p-value <0.05. For each model the reliability (goodness of fit) was quantified using the Hosmer-Lemeshow test [14]. The predicted values from the logistic regression model were used to construct receiver operating characteristic (ROC) curves and to calculate the area under the ROC curves (AUC). The AUC is a suitable parameter to summarize predictive value and can range from 0.5 (no discrimination) to 1.0 (perfect discrimination) [15]. Software used was SPSS version 18.0 (Apache Software Foundation). All p-values are two sided.

Results

We identified 6,614 incident statin users. Mean age was 61 years and 52% were female. Most patients initiated statin treatment with simvastatin or atorvastatin (36%). At inclusion, 31% of patients used a beta blocker (BB) and 14% a calcium channel blocker (CCB) and 31% used either an antiplatelet drug or a coumarin. During follow-up, 4,189 Patients (63%) were nonpersistent. Of the remaining 2,425 continuous statin users, 111 (5%) had a CMA lower than 80% (Table 2). In the nonpersistent group, a smaller proportion was between 50 and 59 years, used atorvastatin and antidiabetics and a larger proportion used coumarins or anti platelet drugs and angiotensin receptor blockers. In the group with poor drug taking compliance, a larger proportion of patients was between 18 and 49 years or between 70 and 79 years of age. A smaller proportion of patients with poor drug taking compliance used anti platelets, coumarins, thiazide diuretics, beta blockers, calcium channel blockers or inhalation drugs (Table 2).

Therapeutic complexity

A statistical significant association between therapeutic complexity and nonpersistence was found for the number of visits, total number of fills, number of single dispensings, number of prescribing physicians and total number of switches within each drug class (Table 3). For drug taking compliance, only the number of single dispensings reached statistical significance. All odds ratios were close to one (Table 3). We had to exclude all variables in the multivariate analysis due to lack of statistical significance, leaving only the results from univariate analysis for further evaluation.

Table 2: Baseline characteristics of the population

Characteristic	Non-persistent N (%)	P-value*	Good drug taking compliance N (%)	Poor drug taking compliance N (%)	P-value*
Overall 6,614 (100)	**4,189 (63)**		**2,314 (95)**	**111 (5)**	
Female sex	2,169 (52)	NS	1,221 (53)	58 (52)	NS
Age (± SD)	61 (12)	NS	61 (11)	56 (11)	NS
18-39 yrs	168 (4)	NS	72(3)	8 (7)	<0.05
40-49 yrs	535 (13)	NS	292 (13)	23 (20)	<0.05
50-59 yrs	1,117 (27)	<0.05	692 (30)	35 (32)	NS
60-69 yrs	1,204 (29)	NS	678 (29)	30 (27)	NS
70-79 yrs	967 (23)	NS	495 (21)	12 (11)	<0.05
80+ yrs	198 (5)	NS	85 (4)	3 (3)	NS
Follow-up (days)	365		365	365	
Statin on inclusion					
Simvastatin	1,504 (36)	NS	798 (34)	47 (43)	NS
Pravastatin	305 (7)	NS	166 (7)	11 (10)	NS
Fluvastatin	25 (1)	NS	16 (1)	1 (1)	NS
Atorvastatin	1,520 (36)	<0.05	911 (39)	36 (32)	NS
Rosuvastatin	835 (20)	NS	423 (18)	16 (14)	NS
Co-medication at index date					
Antidiabetic drug	987 (24)	<0.05	614 (26)	26 (23)	NS
Anti platelet or coumarin	1,357 (32)	<0.05	691 (30)	20 (18)	<0.05
Diuretic	535 (7)	NS	265 (11)	4 (4)	<0.05
Beta blocker	1,336 (32)	NS	700 (30)	22 (20)	<0.05
Calcium Channel Blocker	605 (14)	<0.05	293 (13)	6 (5)	<0.05
RAS Inhibitor	1,111 (27)	NS	571 (25)	19 (17)	NS
Nitrate	212 (5)	NS	102 (4)	6 (5)	NS
Antidepressant	330 (8)	NS	196 (8)	8 (7)	NS
Anxiolytic	317 (8)	NS	172 (7)	14 (13)	<NS
Inhalation medication	278 (7)	NS	140 (6)	1 (1)	<0.05

Abbreviations: RAS Renin Angiotensin System,
* Z-test for proportions, two sided

Table 3: The association between therapeutic complexity and adherence to statin therapy

	Persistent vs. nonpersistent	Mean (±SD)		Good vs. poor drug taking compliance	Mean (±SD)	
Variable*	**OR [95% CI]**	**Persistent**	**Nonpersistent**	**OR [95% CI]**	**Good taking compliance**	**Poor drug taking compliance**
Overall 6,614 (100)		**2,425 (37)**	**4,189 (63)**		**2,314 (95)**	**111 (5)**
Number of visits	1.0 [1.0-1.0]	13.8 (9.6)	14.7 (9.4)	1.0 [1.0-1.0]	13.8 (9.3)	14.2 (13.7)
Number of fills	1.0 [1.0-1.0]	25.1(24.0)	26.8 (22.0)	1.0 1.0-1.0]	25.1 (22.6)	25.7 (45.8)
Number of chronic medication classes	1.0 [1.0-1.0]	3.7 (2.6)	3.9 (3.4)	1.0 [0.9-1.1]	3.7 (2.6)	3.5 (2.6)
Number of single dispensings	1.0 [1.0-1.0]	3.3 (2.2)	3.5 (2.3)	1.1 [1.0-1.2]	3.2 (2.2)	3.7 (2.6)
Refill consolidation	1.2 [1.0-1.5]	0.4 (0.2)	0.4 (0.2)	0.6 [0.3-1.6]	0.4 (0.2)	0.3 (0.19)
Number of dose changes within drug class	1.0 [1.0-1.0]	1.6 (3.4)	1.8 (3.3)	1.0 [1.0-1.1]	1.6 (2.8)	2.3 (9.3)
Number of prescribing physicians	1.0 1.0-1.2]	1.9 (1.0)	2.0 (1.1)	1.0 [0.9-1.2]	1.9 (1.0)	1.9 (0.9)
Total number of switches within each drug class	1.0 [1.0-1.0]	7.9 (6.0)	8.7 (5.7)	1.0 [1.0-1.1]	7.9 (5.5)	8.8 (12.2)

Abbreviations: CI confidence interval, OR odds ratio, SD standard deviation.
*Calculated 12 months before initiation.

Discussion

This study shows that therapeutic complexity is associated with nonpersistence and poor drug-taking compliance. However, odds ratios approach one, indicating a low predictive value. The direction of these findings is in line with the findings of Choudry et al, however the absolute predictive value is less pronounced than the results in the US setting [12]. This indicates that the complexity of the health care system rather than therapeutic complexity itself may have greater impact on both persistence and drug taking compliance. In the Dutch healthcare system a 'pharmacy home' is present for most patients since virtually all patients use a single pharmacy, all prescription medication is captured by the database and hardly any mail-order pharmacies are present [16]. Findings from both Choudry's and our study therefore indicate that medication adherence should be regarded in the context of the local health care system. The Dutch healthcare system represents a system with relatively low complexity for patients to receive and refill prescriptions whereas in the US health care system drug coverage is often 'carved out' and administrated separately from medical benefits. In the US prescriptions are written by multiple prescribers and collected in multiple pharmacies. The latter findings emphasize the creation of a "pharmacy home" in the US and also the prevention of fragmentation of pharmacy services in The Netherlands.

Strength of this study is that we included only patients with a first statin prescription by ensuring that they were eligible in the database in the year before the inclusion and had an initial prescription of ≤15 days. By including only patients with prescriptions 12 months before and after inclusion, we prevented the inclusion of 'pass through', or incidental patients. A possible limitation to our study is that follow-up may have been too short to identify all patients who discontinue statins. Several studies however, both in users of statins and other (cardiovascular) drugs indicate that most patients discontinue treatment in the first twelve months [4, 6], indicating that short follow-up is less likely to be of importance.

Future directions

Refill consolidation showed a nonsignificant 23% increased risk of nonpersistence and remains an interesting variable for further investigation. Refill consolidation is currently the only known factor with potential meaningful predictive properties for medication adherence [12, 17-19]. Refill consolidation is a measure of the degree in which medication is synchronized because it captures the number of different drugs dispensed per pharmacy visit. Intuitively a higher synchronization rate (i.e. high refill consolidation) should correspond to good drug taking compliance and persistence. For other predictors for medication adherence one should probably focus on other patient related factors such as beliefs about medicines that have previously been associated with medication adherence [20, 21].

Conclusion

Therapeutic complexity is associated with nonpersistence and poor drug taking compliance, but odds ratios are small, indicating a low predictive value. A relative simple way to reduce therapeutic complexity is to synchronize prescription refills.

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Chapter 4

Patient beliefs and medication adherence

Early changes in beliefs about new chronic drug therapy and the risk of nonpersistence

Submitted for publication

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Abstract

Background

Beliefs about medication have been shown to be associated with medication adherence. However, it is unclear whether beliefs about chronic medication change over time and to what extent changes in beliefs are associated with adherence. We studied the relationship between patient beliefs and medication adherence among patients initiating new drug treatment.

Methods

Patients with a first prescription for a drug intended for chronic use were identified in 9 pharmacies. All patients received the Beliefs about Medicines Questionnaire specific (BMQs) at the start (t0) and after one (t1) month. Dispensing records were extracted from the pharmacies after 10 months. Nonpersistence, defined as a gap of at least 60 days without medication, was assessed. Patient beliefs were classified as ambivalent (high necessity, high concerns), skeptical (low necessity, high concerns), indifferent (low necessity, low concerns) and accepting (high necessity, low concerns), based on their BMQs scores.

Results

Included were 376 patients. Response rates were 47% and 38% at t0 and t1. Of the responders 58 (33%) were non-persistent. No significant association between beliefs at t0 and persistence was present. However, at t1 an increased risk of nonpersistence was found for indifferent (RR 5.2 [95% CI 1.3-20.6]) and skeptical beliefs (RR 6.6 [95% CI 1.6-26.6]).

Conclusions

Indifferent and skeptical beliefs one month after the start of therapy are associated with increased risk for nonpersistence. Interventions to improve persistence should be focused on indifferent and skeptical patients, during the first month of therapy.

Introduction

Rates of nonadherence with drug therapies are high [1-4]. Adherence can be classified into three phases: acceptance, execution and discontinuation [5]. Acceptance deals with the process of initiation of the drug therapy. Execution refers to the quality of execution of the drug regimen and deals with missing (unintentional) or skipping (intentional) one ore more doses while staying on therapy. Discontinuation deals with the termination of drug therapy, which is also called nonpersistence. Especially at the start of therapy many patients discontinue treatment [1, 6-8]. Medication beliefs are associated with medication adherence [9]. Patients who accept drug therapy are more frequently adherent to their medication regimens than patients who are ambivalent, indifferent or skeptical [10, 11]. Patients starting an antidepressant who disagree with their physician on the indication for the medication were more likely to discontinue antidepressants [1]. Previous studies mostly included patients who were already on therapy and did not specifically investigate patient beliefs at the start of therapy [9]. Moreover it is not known to what extent beliefs on medication change during this acceptance phase. We therefore investigated if attitudes obtained from beliefs about medicines, in new users of five different drug classes, at the start of therapy and after one month were associated with nonpersistence.

Methods

Study design and setting

This prospective cohort study was conducted in nine pharmacies located in rural and urban areas in The Netherlands. Participants were selected from October 2008 to April 2009 and followed for ten months. All pharmacies had real time prescription transfer with the general practitioner, ensuing that all prescriptions from the GP were sent to only one pharmacy. Prescriptions from specialists were transferred to the patient's pharmacy by means of a fax service from the hospital to the pharmacy. At the end of follow-up all medication dispensing records for each individual patient were collected in the participating pharmacies, depending on the date of inclusion, so that follow-up was at least 10 months. Dispensing records contained: the dispensing date, the drug name,

the Anatomical Therapeutical Chemical (ATC) code [12] number of tablets, dosing instructions and prescriber information.

Participants

Participants were ambulant patients with a first prescription, defined as no use in the previous twelve months, for one of the following: (1) statin, (2) cardiovascular drug, (3) bisphosphonate, (4) antidepressant, (5) oral antidiabetic drug. Participants had to be between the age of 18 and 80. Patients were not eligible for participation if: (1) the prescription contained directions 'as needed', (3) the patient used any dosing aids (medication boxes with weekday and time indicators), (4) chronic use was unlikely or was suspected not to be indicated (i.e. tricyclic antidepressant as a sleeping agent, diuretics to treat ankle edema, etc), (5) the patient had his medication dispensed from multiple pharmacies, moved or was hospitalized.

Data collection

All eligible patients were asked to participate in the week after they had received their medication from the pharmacy. Patients were asked to fill in the BMQ-specific questionnaire referring to the drug of inclusion. Questionnaires were sent to the participants at the index date and after one month. Questionnaires were returned to the research site in a toll-free envelope. In case participants did not return the questionnaires within fourteen days, they were reminded by sending them a new questionnaire and by a telephone call three days later.

Ethics and privacy

All personal data were removed except the date of birth, sex, patient-number and pharmacy name. Researchers were then able to link dispensing records to the questionnaires through a unique patient number.
Written approval by the institutional review board of the University Medical Center Utrecht was obtained. Written consent to link the dispensing records to the questionnaire was obtained from each patient.

Variables

Patient beliefs about their medicines were assessed using the BMQs, which has been validated for use in the chronic illness groups studied [9]. The BMQs comprises two five-item scales assessing patient beliefs about the necessity of prescribed medication for controlling their illness and their concerns about taking it. The BMQ uses a 5-point Likert agreement-disagreement scale. Both

the necessity and concerns scales were split at midpoint and scores above midpoint were considered as high and scores below midpoint as low. Patients were then classified in four different categories, corresponding to their attitude as earlier described [10, 11]. In short: accepting (high necessity and low concerns), ambivalent (high necessity and high concerns), skeptical (high concerns and low necessity) and indifferent (low concerns and low necessity).

Outcome variables

Nonpersistence was defined as a gap of at least 60-day after the expiration of the combined previous prescriptions. Using this method we compensate for patients who renew their prescription before their previous prescription has expired [13].

Statistical methods

Baseline characteristics and the classification into attitudes were calculated, using SPSS version 18.0. We calculated the relative risk for nonpersistence for each attitude with the accepting group as the reference group using Microsoft Excel 2004 version 11.5.6 [14]. A sensitivity analysis with gaps of at least 30 days and at least 45 days was done to validate the results.

Results

A total of 376 individuals were eligible for inclusion and received the first questionnaire. Response rates for t0 and t1 were 47% and 38% (Figure 1). Of the initial responders, five questionnaires were incomplete or could not be assessed. Two patients withdrew consent and one moved during the study period.
Baseline characteristics for the responders are presented in Table 1. Most patients received a first prescription for a cardiovascular drug (diuretic, beta blocker, angiotensin converting enzyme inhibitor, calcium channel blocker and angiotensin receptor blocker). Average follow-up was 328 ±18 days. Of the initial responders (t0) 58 (33%) were nonpersistent. Nonpersistence was significantly higher (55%) in the non-responder group (data not shown). No differences in sex and included drug were observed between responders and non-responders, except for bisphosphonates, which were used more often in the responder group (data not shown).

Table 1: Baseline characteristics of responders

Variable	Responder	
	N	%
Total	178	47
Mean age (±SD)	62	12
Female sex	104	58
Oral antidiabetic	9	5
Cardiovascular drug	107	60
Statin	32	18
Bisphosphonate	9	5
Antidepressant	21	12

Abbreviations: SD standard deviation.

In Figure 2 the overall percentage of patients with one of the four possible attitudes at t0 and t1 as well as the nonpersistence rates are presented. In Table 2 the relative risks of becoming nonpersistent for accepting, indifferent, skeptical and ambivalent users at t0 and t1 are presented. There was no significant association between the four different attitudes at t0 and nonpersistence. At one month (t1) however indifferent and skeptical attitudes were significantly associated with nonpersistence. The highest risk for becoming non-persistent was 6.6 (95% CI: 1.6 to 26.6) for skeptical users. Indifferent users had a 5-times increased risk of becoming nonpersistent (Table 2). Results from the sensitivity analysis with gaps of at least 30 days or 45 days gave comparable results compared to a gap of at least 60 days without medication available.

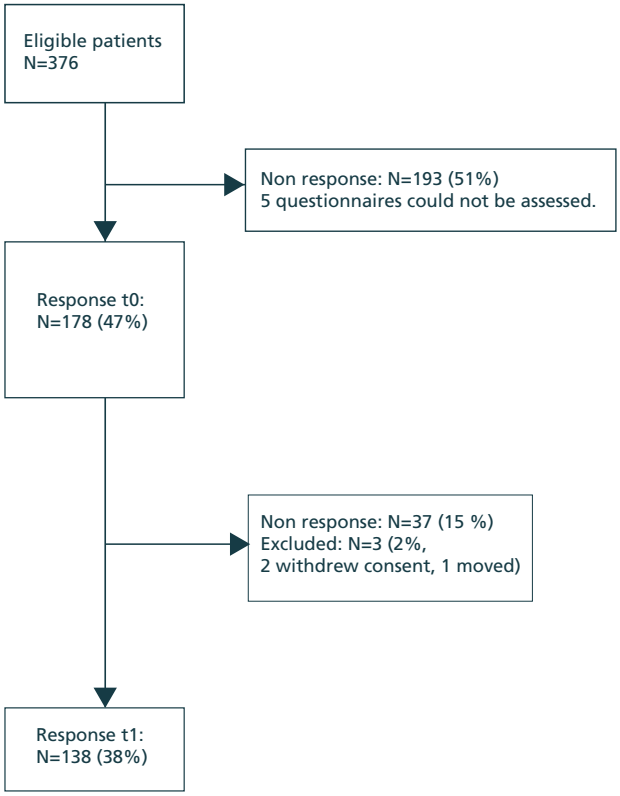

Figure 1: Study flow

Table 2: Patient beliefs about the drug of inclusion at the start of therapy (t0) and after one month (t1) and corresponding relative risk (RR) for nonpersistence

	N	Nonpersistent (%)	RR (95%CI)
At t0	178	29.2	
Accepting (reference group)	23	21.7	1.00
Ambivalent	88	26.1	1.20 (0.51-2.81)
Indifferent	36	47.2	2.17 (0.92-5.08)
Skeptical	31	41.9	1.92 (0.80-4.65)
At t1	138	26.9	
Accepting (reference group)	23	8.0	1.00
Ambivalent	60	26.7	3.33 (0.83-13.44)
Indifferent	34	41.2	5.15 (1.28-20.64)
Skeptical	19	52.6	6.58 (1.63-26.58)

Abbreviations: CI confidence interval, RR Relative risk.

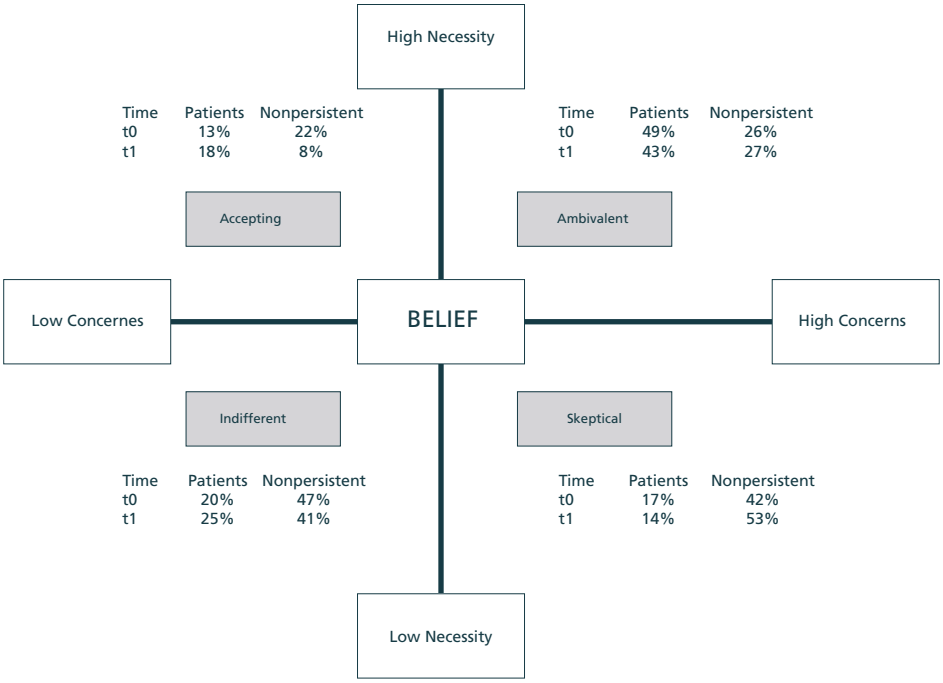

Figure 2: Necessity and concerns domains derived from the BMQ-specific and the subdivision into ambivalent, skeptical, indifferent and accepting attitudes towards chronic medication, the attitudes at the start (t0) and after one month (t1) as well as nonpersistence rates are given for all study participants

Discussion

This study has two important findings. The first finding is that attitudes towards chronic medication at the start of therapy do not predict nonpersistence, but do so after one month. This suggests that patients are going through an appraisal phase during this period. Second, a gradient seems to exist in beliefs. Indifferent beliefs are associated with a lower risk of becoming nonpersistent than skeptical beliefs. This observation is to be expected, since skepticism has both low necessity and high concerns scores compared to indifferent (only low necessity). Indifferent and skeptical users have the highest risk of becoming nonpersistent and both have low necessity scores, we therefore believe that necessity beliefs play a more important role in early persistence than concerns. It is unclear if low necessity scores reflect poor perception of the risks and prognosis associated with the underlying disease or if low scores in nonpersistent patients may be a result of becoming adjusted with their chronic condition. Both may lead to decreased awareness of the importance of drug therapy.
The relation between poor drug taking compliance and necessity beliefs has been studied in several conditions all showing that especially necessity beliefs were low in poor drug taking compliance [10, 15-17].

Limitations and strengths

A limitation of our study is the presence of response bias; responders were more persistent compared to non-responders. We therefore believe that patients included in this study may have had a more positive attitude towards medicines. It is likely that selection, due to response bias, may have resulted in less extreme differences between persistent and nonpersistent patients [18]. This means the results from our study are probably underestimating the real life situation.
This study is to our knowledge the first study that investigated the beliefs about chronic medication at two different time points. Strength of our study is that we used pharmacy data which are an objective way to measure adherence and to avoid possible recollection bias or social desirability [19]. Moreover we performed a sensitivity analysis that revealed comparable relative risks when varying the gap from 30-45 days.

Implications

This study has two useful implications for interventions aimed at improving adherence. First, interventions to improve adherence are more efficient once the researcher, pharmacist, nurse or general practitioner (GP) knows which patients are at risk for nonpersistence. They can focus their interventions on indifferent and skeptical patients. Second, since attitudes towards chronic drug therapy crystallize during the first month of therapy, interventions are probably more successful when employed during the first month of therapy. We believe that most efforts to improve persistence should be done during this period. Interventions to improve persistence should address concerns with chronic drug therapy, but should especially focus on the necessity of drug therapy, since low necessity scores are more strongly associated with nonpersistence. Future studies should investigate whether such an approach is beneficial and which interventions work.

Conclusions

Accepting patients are more likely to continue treatment compared to indifferent and skeptical patients. Health care professionals should focus on indifferent and skeptical patients to improve persistence, the best strategy is to emphasize the necessity of drugs in these patients and do so during the first month of therapy.

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Development of a risk score to predict nonpersistence from patient beliefs and satisfaction with information about medicines

Submitted for publication

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Abstract

Introduction

Nonpersistence to medication is a worldwide problem and many factors possibly predicting nonpersistence have been investigated, but were found to have marginal predictive properties. We aimed to develop an easily applicable risk score to predict nonpersistence.

Methods

In a prospective follow-up study, patients that filled a first prescription for a drug intended for chronic use were included in nine pharmacies in The Netherlands. All patients received a questionnaire at the time of the first prescription (t0) and one month (t1) after the first prescription. The questionnaire consisted of both the Beliefs about Medicines Questionnaire general and specific (BMQ) and the Satisfaction about Information on Medicines Scale (SIMS). Electronic dispensing records were extracted 10 months after inclusion. Nonpersistence was defined as having a 90-day gap in the availability of medication. Multivariable logistic regression models were constructed with nonpersistence as a dependent variable, using the questions at t0 and t1 as covariates. The best predictive model was selected and a risk score was calculated. Sensitivity and specificity positive (PPV) and negative predictive values (NPV) were calculated to determine the optimal cutoff value.

Results

379 patients were eligible to participate in the study. Response rates at t0 and t1 were 49% and 39% respectively. The best model for nonpersistence was found at t1, with the following predicting variables (1) People who take medicines should stop their treatment for a while every now and again, (2) Have you received information what you should do if you experience unwanted effects? (3) 'This medicine has unpleasant side effects'. Sensitivity, specificity, PPV, and NPV were 83%, 66%, 44% and 93% respectively.

Conclusion

Prediction of nonpersistence is possible from beliefs about medicines. The developed risk score could easily be integrated in daily clinical care to assist pharmacists or GP's in identifying patients at risk for nonpersistence.

Introduction

Over 50% of patients are estimated to be nonadherent to their medication. Nonadherence is an important reason why drugs do not have the desired effect and accounts for increased mortality and morbidity as well as increased costs [1, 2]. Adherence can be subdivided into persistence and drug taking compliance [3]. Persistence assesses whether a patient continues therapy or not. Premature discontinuation of therapy is called nonpersistence. Nonpersistence has worse clinical outcomes compared to poor drug taking compliance in most drug categories.

Many items that may predict nonadherence have been studied, but the predictive value of these items is limited. Steiner et al. found that demographic and socioeconomic factors do not predict adherence and Chan et al. found that patient, physician and payment factors were not associated with adherence to statins [4-6]. The only variable found to predict nonadherence was refill consolidation [7]. Psychological factors like beliefs patients have about their medication however are found to correlate well with adherence. However, a model that can predict nonpersistence, with sufficient sensitivity and specificity has not been found yet. The aim of our study was to investigate whether beliefs about medicines and satisfaction about the information about medicines could be used to construct a predictive model for nonpersistence.

Methods

Study design and setting

This prospective cohort study was conducted in a central area in The Netherlands with both rural and more urban areas. Participants were selected from October 2008 to April 2009 in nine participating pharmacies and followed for at least ten months. All pharmacies had real time prescription transfer with the general practitioner, ensuing that all prescriptions from the GP were sent to only one pharmacy. Prescriptions from specialist were transferred to the patient's pharmacy by means of a fax service from the hospital to the pharmacy. This also ensures that all written out prescriptions were collected in the patient's own pharmacy. From all prescriptions dispensed, the dispensing date, the Anatomical Therapeutical Chemical (ATC) code, quantity dispensed and dosing instructions were registered in the participating pharmacies' information

systems. Ten months after inclusion in the study all medication histories were extracted from the pharmacies' electronic records

Participants

Participants were all patients with a first prescription for one of the following: statin, cardiovascular drug, bisphosphonate, antidepressant, or an oral antidiabetic drug. Participants had to be between the age of 18 and 80. Patients were not eligible for participation if (1) the prescription contained directions "as needed", (2) a drug from the same therapeutic class was used in the previous twelve months, (3) the patient was not ambulant, (4) the patient used a dosing aid (i.e. a medication weekbox), (5) the drug had a non-chronic indication (i.e. tricyclic antidepressant as sleeping agent, diuretics to treat ankle oedema, etc), (6) the patient also purchased some of his medication in other pharmacies than the participating pharmacies, was hospitalized or temporarily moved to another address in the ten months following the index date, (7) the patient used monthly bisphosphonate formulations.
Add-on therapy (e.g. addition of an angiotensin converting enzyme -ACE- inhibitor to a diuretic) was considered as a new prescription. Switches between different therapeutic classes (e.g. switch from a diuretic to a beta blocker) were considered as a new prescription.

Data collection

All eligible patients were asked to participate within a week after receiving a first prescription from the pharmacy. Patients received a validated Dutch translation of the Satisfaction with Information about Medicines Scale (SIMS) [8], two validated Dutch translations of the Beliefs about Medicine Questionnaire (BMQ), and the BMQ-specific, which refers to the drug of inclusion and the BMQ-general, which investigates the patient's general beliefs about medication [9]. The SIMS questionnaire assesses the satisfaction of patients with the information received about their medicines. Besides the SIMS and BMQ, the following two additional questions were asked: (1) 'Do you use any herbal or homeopathic drugs next to your prescribed medication?' (2) 'How long do you believe you have to take the prescribed drug you just received in your pharmacy? Please answer in days, weeks, months, years, lifelong or don't know.' At every questionnaire we added an additional question to evaluate whether the patient stopped taking the drug under investigation or not. Questionnaires were sent to the participants at the index date (t0) and after one (t1) month

and were returned to the research site in a toll free envelope. If fourteen days after the first prescription, participants had not returned the questionnaires, they were reminded by sending them a new questionnaire and with a telephone call three days later. All personal data were eliminated except the date of birth, sex, patient-number and pharmacy name. Researchers were then able to anonymously link questionnaires to corresponding medication histories. Ten months after the index date, complete medication histories were extracted from the pharmacy database. Written approval of the medical ethical evaluation board of the University Medical Center Utrecht was obtained. Written consent to link the medication histories to the questionnaire answers was obtained from each patient.

Variables

Predictor variables were answers to all individual questions and all composite sub-components from the BMQg, BMQs and SIMS.

The BMQ-general has two sub-components (four statements each): 'general-overuse', which relates to beliefs that medicines are generally being overused by doctors, and 'general-harm', which relates to beliefs that medicines are generally potentially harmful and addictive. Respondents indicate their degree of agreement with each individual statement about medicines on a five-point Likert scale, ranging from 1=strongly disagree to 5=strongly agree. Scores obtained for the individual items within each scale are summed to give a scale score. The scores range from 4-20 for each sub-component.

Patient beliefs about the specific medicines they received were assessed using the BMQs, which has been validated for use in the chronic illness groups studied [9]. The BMQs comprises two five-item sub-components assessing respectively patient beliefs about the necessity of prescribed medication for controlling their illness and their concerns about the potential adverse consequences of taking it. It is calculated in the same way as the BMQg. Thus, total scores for the necessity and concerns sub-components range from 5 to 25. The calculated difference between necessity and concerns scores has a possible range of −20 to 20. The necessity–concerns differential may be thought of as the result of a risk–benefit analysis for each patient in whom their perceptions of risk (concerns) are weighed against their perception of benefit (necessity beliefs). If the difference is positive, the patient perceives that the benefits of medication outweigh the risks. Conversely, if it is negative, the patient perceives greater risk than benefit. The SIMS is a validated 17-item questionnaire, in which each item refers to

a particular aspect of medicines. Participants are asked to rate the amount of information they have received using the following response scale: 'too much', 'about right', 'too little', 'none received' and 'non needed'. A total satisfaction rating can be obtained by summing the scores of each item. If the patient is satisfied that he/she has received a particular aspect of medication information (with a rating of 'about right' or 'non needed'), this is given a score of 1. If the patient is dissatisfied with the amount of information received (with the rating scales: 'too much', 'too little', or 'non received'), this is scored 0. Scores range from 0-17, with higher scores indicating a higher degree of satisfaction. A subcomponent of the first 9 items identifies patient's satisfaction with information about the action and usage of medication and a subcomponent with the last 8 items identifies satisfaction with information about potential problems of medication. Higher levels of satisfaction are related to better self reported adherence [8].

The answer to the question about the homeopathic or herbal medicine was assessed as a dichotomous value, with 'yes' or 'no' as possible answers. The question about the duration of therapy could be answered in days, weeks, months and years and was corrected for the 'I don't know answer' by including the latter question in the model as a dummy variable.

Outcome variables

Nonpersistence was defined as a gap of at least 90 days of non-use after the expiration of the combined previous prescriptions. Using this method we compensate for patients who renew their prescription before their old prescriptions have expired, accounting for stockpiling [10].

Statistical methods

Characteristics of the study population at the index date were analyzed using the independent sample t-test or z-test for proportions if appropriate.

Strength of association with nonpersistence was expressed as odds ratios for all potential predictive variables at t0 and t1. Logistic regression with nonpersistence as the dependent variable was tested with all potential predictive variables as the covariates. All covariates from the univariate regression analysis with a p-value <0.10 were included in a multivariate logistic regression analysis. We excluded the variable with the highest p-value every run, until all variables had a p-value <0.05. The predicted values from the logistic regression model were used to construct receiver operating characteristic (ROC) curves and

to calculate the area under the ROC curves (AUC). The AUC or C-statistic is a suitable parameter to summarize discriminative or predictive value and can range from 0.5 (no discrimination) to 1.0 (perfect discrimination). The Hosmer-Lemeshow statistic, indicating the goodness of fit, was calculated for each model. The adjusted regression coefficients of the model were multiplied by a factor 10 and rounded to the nearest integer to obtain an individual risk score for each predictor. If predictors showed a negative association with nonpersistence, we recoded the variable to obtain a positive association. The total risk score was calculated for each patient by assigning points for each predictor present and if applicable by multiplying it with the "Likert score" and then adding all points. Multiplication was necessary because the risk score obtained with logistic regression represents the score per "unit Likert score", BMQ-questions have a five point (Likert) scale whereas SIMS questions have a dichotomous scale. The risk score was normalized to a scale ranging from 1 to 100 for between model comparison. The total scores were subdivided and sensitivity (the chance of detecting nonpersistence if present), specificity (the chance of ruling out nonpersistence when absent), positive predictive values (the relative frequency of the model being correct) and negative predictive values (the relative frequency of not being nonpersistent if the model predicts so) of the risk score were calculated for the different cut-off values. Software used was SPSS for Windows, version 18.0 (Apache Software Foundation). All p-values are two sided.

Results

Baseline characteristics

A total of 376 individuals were eligible for inclusion and received the first questionnaire. Response rates for t0 and t1 were 49% and 39%. 8 Patients were lost to follow-up or excluded; five t0-questionnaires could not be assessed, two patients withdrew consent after receiving the t1-questionnaire and one moved (Figure 1).

Baseline characteristics of the responders at t0 are presented in Table 1. Most patients received a first prescription for cardiovascular drugs (e.g. diuretics, beta blockers, angiotensin converting enzyme inhibitors). Average follow-up was 328 (±18) days. Of the 178 responders, 51 (28.7%) were nonpersistent. Antidepressants were used more often in nonpersistent patients. Nonpersistent patients had lower satisfaction with the information they received about their medication and lower necessity scores on the BMQs (Table 1).

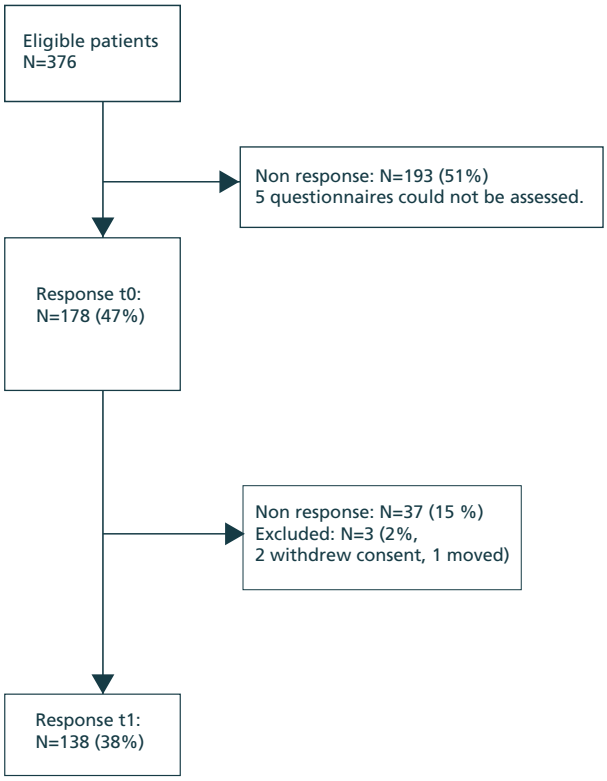

Figure 1: Study flow

Table 1: Baseline characteristics of responders at t0

Variable	Persistent, N=127 N (%)	Nonpersistent, N=51, N (%)	p-value
Mean Age (SD)	62 (12)	62 (12)	NS
Female sex	52 (41)	22 (43)	NS
Antidiabetic drug	8 (6)	1 (2)	NS
Cardiovascular drug	81 (64)	26 (51)	NS
Statin	23 (18)	9 (18)	NS
Bisphosphonate	6 (5)	3 (6)	NS
Antidepressant	9 (7)	12 (24)	<0.05
t0			
BMQ overuse	11.3 (2.5)	11.5 (2.8)	NS
BMQ harm	9.8 (2.2)	10.4 (2.2)	NS
BMQ general	21.1 (3.9)	21.9 (4.3)	NS
SIMS action	6.5 (2.4)	6.1 (2.7)	NS
SIMS problems	8.1 (3.2)	7.2 (3.1)	NS
SIMS total	14.6 (5.0)*	13.1 (4.8)*	NS
BMQs concerns	14.1 (3.2)	14.3 (3.3)	NS
BMQs necessity	16.2 (3.6)	15.0 (4.5)	NS
BMQs differential	2.1 (4.2)*	0.9 (4.3)*	NS
t1			
BMQ overuse	11.4 (2.4)	11.1 (2.7)	NS
BMQ harm	9.8 (2.1)	10.7 (1.9)	0.05
BMQ general	21.2 (3.9)*	21.9 (4.0)*	NS
SIMS action	6.4 (2.5)	5.7 (2.9)	NS
SIMS problems	8.3 (3.2)	6.5 (3.0)	0.05
SIMS total	14.8 (5.4)*	12.0 (5.5)*	0.02
BMQs concerns	13.5 (3.0)	14.3 (3.1)	NS
BMQs necessity	16.4 (3.6)	14.7 (3.1)	0.05
BMQs differential	2.9 (4.0)*	0.4 (4.2)*	<0.01

Abbreviations: SD standard deviation; BMQ beliefs about medicines questionnaire, SIMS satisfaction with information about medicines scale, BMQs beliefs about medicines questionnaire specific, NS not significant.

* Total scores are not exactly the total of the mean domains, because of missing or inevaluable answers in the individual questions of the domains.

Predictive model

For nonpersistence a multivariate logistic regression model could be constructed at t0 and t1. The best performing model for nonpersistence was at t1. The C-statistics at t0 and t1were 0.7 and 0.8 respectively for both multivariate models predicting nonpersistence (Table 2). The Hosmer-Lemeshow statistic for all models indicated that the fit of the model was good.

The significant predictors for both multivariate models are presented in Table 2, at t1, nonpersistence was predicted by three items from the questionnaires. For both models beliefs that medicines had unpleasant side effects were an important predictor (Table 2). The risk score displayed represents the value of one unit in the scale used to measure the corresponding item. For example the SIMS variables are dichotomous and the score is either granted or not, while the BMQ variables have five possible answers (ranging from 1 to 5). As a result, the risk score may have to be multiplied by five if the answer is "strongly agree" or by three if the answer is neutral. So if a patient strongly agrees (score=5 out of 5) that his treatment should be interrupted for a while every now and then, if he has received too little information about what to do when side effects occur (score=1 out of 1) and if he strongly disagrees that his medication has unpleasant side effects (score=1 out of 5), his total risk score is calculated as followed: risk score for nonpersistence =(5*10)+(1*18)+(1*8)= 76 (Table 2).

Table 3 displays the risk scores and the corresponding sensitivity, specificity, positive predictive (PPV) and negative predictive value (NPV) for nonpersistence at t1, since this was the best predicting model (highest C-statistic). The range in risk scores for nonpersistence was 18 to 100 at t1, Best cutoff value for nonpersistence at t1 was at a risk score of 59, resulting in a sensitivity of 83%, specificity of 66%, PPV of 43% and NPV 92% (Table 3).

Table 2: Individual variables of the multivariate model fornonpersistence and their corresponding risk scores at t0 and t1

Time	C-statistic	[95%CI]	Predictor	Risk score
t0	0.74	[0.65-0.83]	'This medicine has unpleasant side effects.'	14
			'How long do you believe you have to take the prescribed drug you just received in your pharmacy?'* ('Years', 'life-long')	29
t1	0.81	[0.72-0.90]	'People who take medicines should stop their treatment for a while every now and again'	10
			'Have you received information what you should do if you experience unwanted effects?'* ('Not-received', 'too little', 'too much')	18
			'This medicine has unpleasant side effects.'	8

Abbreviations: CI confidence interval
* Answers were dichotomous, a score was either granted or not. All other variable scores have a range from 1 to 5 and the models' risk score has to be multiplied by the score assigned to the answer the patient gave.

Table 3: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at the different risk scores for the predictive model for nonpersistence at t1

Risk score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
18	100.0	1.1	24.2	100.0
26	100.0	4.2	24.8	100.0
34	100.0	11.6	26.3	100.0
42	96.7	26.3	29.3	96.2
51	86.7	39.0	31.0	94.2
59	83.3	66.3	43.9	92.7
67	63.3	82.1	52.8	87.6
75	46.7	95.8	77.8	85.1
84	10.0	95.8	42.9	77.1
92	0.0	99.0	0.0	75.8
100	0.0	100.0	0.0	76.0

Abbreviations: PPV positive predictive value; NPV negative predictive value.

Discussion

This study shows that beliefs and satisfaction with knowledge about chronically intended medication predict future nonpersistence. We found that the best timing to predict future nonpersistence is at one month after start of therapy. Sensitivity and specificity are reasonably high with a good fit for both models. At the proposed cutoff values, PPV was about 43%. This indicates that other factors than beliefs and satisfaction on information influence patient adherence. We found high NPV (about 90-95%) at the proposed cutoff value, indicating that patients with a low risk score indeed have a small chance of becoming nonpersistent. The latter makes this model particularly attractive to assess which patients need an intervention to improve persistence and in which patients the risk of becoming nonpersistent is low. We found that only three items could be characterized as predictive variables for nonpersistence we therefore believe it is feasible to implement a combined model in daily clinical practice.
Although overall patients who discontinue treatment have lower scores on the BMQ necessity domain, neither this domain nor individual questions from this domain were predictive for nonpersistence. This suggests that concerns and especially the occurrence of side effects is a more important predictor for nonpersistence than beliefs about the necessity of therapy.

Limitations and strengths

A limitation to our study is that no external validation of the model was done. We encourage validation of the model in a different population, because this will answer if the proposed model will perform as well in comparable patients and can be generalized [11].
To our knowledge this is the first study that prospectively investigates the prediction of nonpersistence at different points in time based on the thoughts and beliefs of patients about their medicines, providing a predictive model that can be employed in daily clinical practice.

Comparison with other studies

Many predictors of medication nonadherence have been investigated; in a recent study Steiner et al. concluded: "Sociodemographic and clinical characteristics are not clinically useful predictors of refill adherence in patients with hypertension" [4]. Chan et al. found that patient, physician and payment factors could not predict adherence to statins [5]. Choudhry et al. observed a relation between adherence and therapeutic complexity, although these findings could not be replicated in The Netherlands [7, 12]. Variables in all these studies have not included patient beliefs towards chronic medication. Byrne and colleagues found that illness perception did not prove helpful in predicting secondary preventive behavior among patients with coronary heart disease, but beliefs about medication appeared to be reasonable predictive of medication adherence [13]. Horne and Weinman showed that beliefs and especially the necessity concerns differential were related to self-reported medication adherence [9]. Menckeberg showed a more objective relation between reported beliefs about medicines and adherence calculated from medication dispensing records [14].

Clinical implications of this study

Although there was limited difference in the calculated total scores between persistent and nonpersistent patients, individual questions from both questionnaires provided a predictive model. The NPV was high, indicating that patients scoring under the cutoff value are unlikely to become nonpersistent. The proposed models provide a tool, which helps both adherence researchers and healthcare workers like pharmacists and GP's to discriminate between patients with a low risk of becoming nonpersistent and patients with a high risk of becoming nonpersistent. The latter will improve the efficiency of care because the (costly) intervention can be focused on those patients that are most likely to become nonpersistent. It is feasible to implement our model in daily clinical practice, since administering the questions from this model is not time consuming. Integrating the proposed model in an ICT program would facilitate healthcare providers like pharmacists and GP's.

Future research should focus on external validation of the predictive model and in testing the effectiveness of implementation of the proposed model by pharmacists or GP's. In those patients with higher scores than the proposed cutoff values pharmacists or GP's should address issues of concern with the patient.

Conclusions

Prediction of nonpersistence is possible from beliefs and satisfaction with information about medicines. The predicting variables for nonpersistence provide a readily applicable risk score model.

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Difference in persistence rates between responders and non-responders to mailed questionnaires

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Abstract

Introduction

Nonpersistence with chronic drug therapy is an important cause of failure of drug therapy. A pitfall in prospective observational studies on medication adherence is selection bias. We investigated whether non-response to mailed questionnaires was associated with nonpersistence.

Methods

In a prospective follow-up study, patients were included in nine pharmacies in The Netherlands and were eligible for inclusion if they filled a first prescription for a drug intended for chronic use. All patients received a questionnaire concerning their beliefs about medicines as well as their satisfaction about the information on medicines. Questionnaires were mailed at the time of the first prescription (t0). Electronic dispensing records were extracted from the pharmacies 10 months after inclusion. Nonpersistence was defined as having at least a 60-day gap in the availability of medication. A Cox proportional hazards model was used to evaluate the association between response and persistence

Results

Of the 355 eligible patients response rate at t0 was 50% and non-response was associated with a 1.85 fold increased risk of nonpersistence. Response time was not associated with nonpersistence. Nonpersistence was 33% in responders and 55% in non-responders.

Conclusions

Responders to a mailed questionnaire showed better persistence.
Researchers should take this selection bias into account in observational studies on medication adherence. Healthcare workers should focus on non-responders to improve persistence.

Introduction

Patients who volunteer to participate in research studies are likely to be different from patients who do not agree to participate. Several studies have shown participants in both observational studies and interventional studies to differ from non-participants on a number of characteristics such as health, gender and income. This implies that the inclusion of patients in a study may lead to selection of patients with healthier behavior [1-4]. In randomized clinical trials (RCT) that evaluate new drugs or the effects of behavioral interventions this type of selection is less problematic and sometimes even favorable. When the purpose of a RCT is to evaluate the effectiveness of a drug or behavioral intervention. Selection of adherent participants will increase the likelihood of proving that the intervention is effective. In studies investigating adherence to drug therapy as the main outcome however, selection of relatively adherent patients will make it more difficult to evaluate the effectiveness of an intervention [5].

In a systematic review we found that self-reported adherence to statins was better compared to adherence calculated from a database. Comparable results were reported from a meta-analysis of studies in ambulatory users of anti osteoporotic medication [6]. In database studies, patients do not have the choice to participate in a study or not, because dispensing data are collected independent from whether a patient is a participant in a study or not. Adherence calculated from a database may therefore be a good source to evaluate whether differences in adherence exist in patients who participate in an experiment and those that do not.

We investigated if the response and response time to mailed questionnaires was associated with medication adherence evaluated by electronic medication histories.

Methods

Study design and setting

This prospective cohort study was conducted in nine pharmacies located in rural and urban areas in The Netherlands. Participants were selected from October 2008 to April 2009 and followed for ten months. All pharmacies had real time prescription transfer with the general practitioner, ensuing that all prescriptions from the GP were send to only one pharmacy. Prescriptions from specialists were transferred to the patient's pharmacy by means of a fax service from the hospital to the pharmacy. From all prescriptions dispensed in the participating pharmacies, the dispensing date, the Anatomical Therapeutical Chemical (ATC) code, quantity dispensed and dosing instructions were registered in the pharmacies' information system.

Participants

Participants were all patients with a first prescription for one of the following: (1) statin, (2) cardiovascular drug, (3) bisphosphonate, (4) antidepressant, (5) oral antidiabetic drug. Participants had to be between the age of 18 and 80. Patients were not eligible for participation if (1) the prescription contained directions 'as needed', (2) a drug from the same therapeutic class was used in the previous twelve months, (3) the patient was not ambulant, (4) the patient used a dosing aid (i.e. a medication weekbox), (5) the drug was prescribed for a non-chronic indication (i.e. tricyclic antidepressant as sleeping agent, diuretics to treat ankle oedema, etc), (6) the patient also purchased some of his medication in other pharmacies than the participating pharmacies, was hospitalized or temporarily moved to another address in ten months following the index date, (7) the patient used monthly bisphosphonate formulations.
Add-on therapy (e.g. addition of an angiotensin converting enzyme -ACE- inhibitor to a diuretic) was considered as a new prescription. Switches between different therapeutic classes (e.g. switch from a diuretic to a beta blocker) were considered a new prescription.

Data collection

All eligible patients were asked to participate within a week after receiving a first prescription from the pharmacy. A questionnaire that asked about the satisfaction with the information patients received about their medication as well as their believes about medication was mailed to the participants at the

index date (t0). In case participants had not returned the questionnaires within fourteen days, they were reminded by sending them a new questionnaire. Ten months after the index date, the complete medication histories of all eligible patients that were extracted from the pharmacy database, and anonymized. Written approval of the medical ethical evaluation board of the University Medical Center Utrecht was obtained.

Variables

For every patient the response, response time, age, sex and therapeutic class of the drug they used were selected as variables. The outcome, nonpersistence, was defined as a gap of at least 60 days after the expiration of the combined previous prescriptions. Using this method we compensate for patients who renew their prescription before their previous prescription has expired [7].

Statistical Methods

Descriptive statistics were used for the baseline characteristics. A Students' t-test was used to assess the difference in response time between persistent and nonpersistent users. A Cox Proportional Hazards model was used to assess the effect of response on the incidence of nonpersistence. We adjusted for age, sex and drug class. We used R software (Austria, www.R-project.org) for all analyses.

Results

The baseline characteristics of the included patients are presented in Table 1. A total of 355 patients were eligible for inclusion. Most patients were women and mean age was 60 years. Of the eligible patients, 178 (50%) responded by sending in the questionnaires. The mean time in which a questionnaire was returned was 19 days (Table 2). Nonpersistence was 55% in patients without any response at t0 and 33% in responders. The hazard ratio for non-responders to become nonpersistent was 1.9 [95% CI: 1.3-2.6] compared to responders. No differences between persistent and nonpersistent users were observed for response time (data not shown).

Table 1: Baseline characteristics

Variable	N (%) N=355
Mean age years (SD)	60 (14)
Female sex	205 (58)
Antidiabetic	20 (6)
Cardiovascular drug	203 (57)
Statin	60 (17)
Bisphosphonate	10 (3)
Antidepressant	62 (17)

Abbreviations: SD standard deviation.

Table 2: Number of responders, mean response time and persistence

Characteristic	N (%) N= 355
Response	178 (50)
Response time in days (SD)	19 (13)
Persistent	199 (56)
Nonpersistent	156 (43)

Abbreviations: SD standard deviation.

Discussion

This study shows that non-response was associated with an increased hazard ratio for nonpersistence (HR=1.9). This suggests that patients who respond are more likely to be persistent. Since the data used for measuring (non)persistence were obtained from the participant's pharmacy, we believe that this study shows that prospective studies using questionnaires, are prone to select more adherent patients. Riekert et al. found that non-response to questionnaires was associated with lower adherence scores measured using structured interviews in patients with diabetes [8]. The difference in scores however were much lower than in

our study, probably because structured interviews are prone to social desirability bias [9]. So the results of the Riekert study probably underestimate selection bias. Gadkari et al. found that non-responders to a medication beliefs survey had 8.2% lower persistence compared to responders [5]. The latter study was comparable to our study and was also evaluated using pharmacy claims and a 60-day gap between two fills as cutoff value for nonpersistence. Nonpersistence in the Gadkari study was 66.3% in the non-responders compared to 58.1% in the responders [5]. The difference between persistence in responders and non-responders was 17% in our study. A possible explanation for the larger observed difference in nonpersistence between responders and non-responders in our study may be caused by the higher response rate, which was 50% compared to 24% in study by Gadkari et al. Sending out a reminder after 14 days may have increased the response rate in our study, since no reminder was send by Gadkari et al.

Limitations and strengths

McGinnis et al. found that both discontinuation and adherence are overestimated in prescription databases, because as much as 50% of patients classified as being nonadherent, have reasons for discontinuation [10]. Overestimation due to planned discontinuation (i.e. discontinuation with a reason) could not be assessed in our study, but it is likely that results reported in our study are also overestimated due to this phenomenon. However, discontinuation in concordance with the prescriber is likely to be equally distributed between responders and non-responders and is therefore unlikely to have influenced our results.

Strength of this study is that we used very reliable dispensing data from the patients' own pharmacy, because almost 99% of the patients in The Netherlands use a single pharmacy [11]. We further prevented misclassification by excluding all patients who moved, picked up prescriptions at other pharmacies or were hospitalized.

Conclusions

Nonpersistence is increased in non-responders to mailed questionnaires. Both researchers and healthcare workers should therefore also focus on the group of non-responders.

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Chapter 5

General Discussion

General discussion

In the introduction of this thesis we asked ourselves whether differences in measurement and reporting influence adherence outcomes. We have investigated if nonpersistence and poor drug taking compliance could be predicted from historical dispensing data and lastly, we have investigated if beliefs about medicines were associated with adherence to chronic therapy. The final Chapter of this thesis discusses the findings of the studies and places them in a broader context. Recommendations for interventions to improve adherence in clinical practice as well as for future adherence studies are made. We start with recommendations of reporting, measurement definitions and cutoff values in adherence. We then focus on the prediction of (non)adherence from historical data and beliefs about medicines. Finally we discuss the role of the pharmacist in adherence, propose a framework for interventions to improve adherence and discuss the influence of nonadherence on value in health care.

Reporting and measurement of nonadherence

Terms used in the literature

In literature, the terms adherence, compliance, persistence, concordance and pharmionics are all used to describe to what extent actual patterns of drug use match the originally intended treatment plans [1-3]. Of these terms compliance has been longest in use to describe the extent to which patients follow prescribed dosing regimens. However, compliance is an obedience-based approach - assuming that the prescriber knows what is best - and in general, non-compliance is considered erroneous patient behavior. Therefore it is generally preferred to use the term adherence as a blanket term for the description of the patient's drug utilisation patterns. Adherence is a blanket term, which is both used to refer to persistence and to taking compliance. Persistence is a measure of duration of time during which a patient is continuing to use the prescribed medication. A patient may be persistent but not be taking the

medication on a regular basis or in another way than intended. Therefore we reintroduce compliance but only in relation to drug taking behavior. Taking compliance describes the way the patient is actually using the medication. Drug taking compliance and persistence are different phenomena and have different clinical and economical consequences and are likely to be driven by different behavioral mechanisms. The most recent addition to adherence terminology is concordance. Concordance is a new way to define the process of successful prescribing and drug taking, based on partnership. Concordance refers to the creation of an agreement about whether, when, and how medicines are to be taken, that respects the beliefs and wishes of the patient [4-6]. The outcome of a concordant agreement between a patient and his health care providers can actually be that a patient will not take his medicines. In contrast to persistence and drug taking compliance, concordance cannot (yet) be measured or quantified.

Recommendation for reporting of adherence

After reviewing the literature (Chapter 2.1) on adherence to statins in ambulatory patients we found that the difference in reporting of adherence resulted in a marked variety of reported outcomes for both poor drug taking compliance and nonpersistence. In studies reporting nonadherence, discrimination between poor drug taking compliance and nonpersistence should be made. Studies that differentiate between poor drug taking compliance and nonpersistence, showed lower nonadherence rates (-14% and -19% respectively) compared to studies that do not differentiate. We believe results from our review on statins can be generalized to reporting of adherence to other chronic drugs. The World Health Organization reports that nonadherence is as high as 50%, but one has to realize that this outcome is an aggregated measure of both nonpersistence and poor drug taking compliance [7] and should therefore be interpreted carefully underlined by the results from our systematic review and meta-analysis (Chapter 2.1). Standardization in reporting of adherence should therefore be encouraged as is done by both the International Society for Pharmacoeconomics and Outcome Research (ISPOR) and the Ascerting Barriers for Compliance (ABC) project (www.abcproject.eu) [3]. The first and easiest step in standardization of reporting should be the discrimination between poor taking compliance and nonpersistence.

How should adherence be measured

Next to discriminating the type of nonadherence, measurement methods have the most influential effect on adherence estimates. Self-reports result in better adherence estimates compared to reported outcomes from databases, especially for nonpersistence. Self-report is probably prone to social desirability and selection bias compared to databases. Adherence estimates from databases use medication refills as a proxy and have a wide range of methodological problems. Reported adherence outcomes are strongly influenced by operational definitions and cutoff values (Chapter 2.1 and 2.2). Estimation of nonadherence from databases, like prescribing, dispensing or reimbursement data uses readily available sources and is therefore relatively cheap. Moreover using databases is only way to estimate adherence on a population level and even health care providers such as pharmacists can apply this methodology to identify nonadherent patients. Self-reported adherence could be used in addition to database findings and to obtain additional information on drug utilization from the patient [8, 9]. Electronic monitoring is especially useful to further investigate specific patterns of taking compliance (e.g. patient forgets his medication mostly during the evening or in weekends). These patterns may be discussed between health care providers and the patient and can help to propose possible solutions (e.g. adaptation of drug regimens or switching to longer acting drugs) to improve adherence [10]. Patient interviews and especially electronic monitoring are both more time consuming and relatively expensive. An approach that limits the use of these techniques to patients suspected for nonadherence can make these more cost and time efficient.

Recommendation for operational definitions in databases

Studies in this thesis showed that the use of different operational definitions results in a broad range of reported adherence outcomes (Chapter 2.1 and 2.2). Hess et al. observed that taking compliance measured within the same cohort, using different operational definitions, give different outcomes for taking compliance [11]. Standardizing operational definitions is difficult, because information captured in databases may not be identical. Some databases may lack the information of the prescribed daily dose (PDD), making it impossible to use measurements based on the Medication Possession Ratio (MPR) measurement methods. In databases that do capture PDD it is recommended to standardize measurement methods, because this would facilitate between study comparisons. Moreover it might be helpful when researchers would use a least

two different operational definitions based on both MPR and the Proportion of Days Covered (PDC) because these are used most often in studies.
Establishment of nonpersistence is mostly based on the presence of gaps without medication available. Although we believe this is an appropriate method, it is important to realize that medication can be restarted at any moment after a predefined gap. In hypertension about 22% of the patients restarted antihypertensive treatment during a ten-year period [12]. In statins 48% of the initially nonpersistent patients restarted therapy in the second year of therapy [13]. In a long-term study among users of inhaled corticosteroids 69% of patients had medication gaps of 1 up to 8 years [14]. Long drug holiday have possible detrimental effects on outcomes of pharmacotherapy [15, 16]. This implies that health care workers should include all patients that are considered to be nonpersistent in their study and should choose cutoff values to define nonpersistence well (see next section).

Recommendation for the use of cutoff values in databases

Reported nonpersistence is strongly influenced by the gap length chosen to discriminate between persistence and nonpersistence. Gap lengths should be sufficiently long so that non-availability of medication is clinically important. It is also important to assess the medication a patient still has in stock, especially if short gaps are of clinical importance (Chapter 2.2).
Cutoff values in taking compliance are more or less standardized because almost every study uses a cutoff value of 80%. We believe that choosing an arbitrarily cutoff value is not correct. Cutoff values to discriminate between poor drug taking compliance and good taking compliance should be based on forgiveness of the drug. Forgiveness is the time resulting from the duration of action of a drug minus its dosing frequency. Forgiveness depends on pharmacokinetic and also pharmacodynamic properties of a drug. Acetylsalicylic acid (ASA) is an example of a drug with high forgiveness, because ASA's irreversible acetylation of platelet cyclooygenase and the consequent reduced formation of thromboxane A2 (TXA2) leads to prolonged bleeding time until production of unmodified platelets occurs. Using a cutoff value for poor drug taking compliance of ASA based on an MPR of 80% is not logical, because patients may still have adequate antiplatelet activity if they forget two tablets of ASA every ten days (MPR=80%) [17, 18]. Drugs like short acting serotonin reuptake inhibitors (SSRI's) or beta blockers have a relative short duration of action and can give rebound symptoms when not taken. Missing 2 tablets every 10 days could lead to clinically relevant withdrawal symptoms [19]. Even within a drug forgiveness

could be dependent on the indication for use. Statins could be relatively forgiving in primary prevention, where the lipid lowering action might be predominant. In patients with acute coronary syndromes pleiotropic' effects of statins on platelet aggregation, smooth muscle cell proliferation, inflammation, and endothelial cell function might be more important and irregular use might be less forgiving [20]. We therefore believe a more rational cutoff value should be chosen to discriminate between poor and good taking compliance. A value based on forgiveness should be a good starting point. Thus more research into the field of forgiveness is needed.

Predictors and prediction of nonadherence

Predictors from historical dispensingdata

As nonadherence is a major cause of drug therapy failure [7], it is essential to identify predictors of early nonadherent behavior. Early identification of potential nonadherent patients will allow healthcare providers to adapt patient counseling early during the course of therapy and may prevent waste of resources due to ineffective drug therapy. Many different predictors have been identified in the literature, most of them obtained from historical data, some directly from patients [21, 22]. Historical data can sometimes be obtained from prescribing or dispensing databases and analyzed using computer algorithms [23, 24]. However the predictive value of these data appears to be limited. Steiner et al. showed that sociodemographic and clinical characteristics do not give a clinically relevant prediction of refill adherence in patients with hypertension [21]. Chan et al. suggest that patient, physician and reimbursement status do not predict adherence to statin therapy [22]. Moreover, Steiner discourages the search for such predictors in an accompanying editorial [25]. An attempt to identify therapeutic complexity as a predictor for nonadherence from historical pharmacy data was successful identifying lack of refill consolidation (a measure for synchronization of medication) as the predominant predictor for nonadherence [26]. This finding that therapeutic complexity leads to increased risk of nonadherence led to recommendations, such as the creation of a 'pharmacy home' and reduction of co-payment. In The Netherlands virtually all patients patronize a single pharmacy and currently almost no co-payment exists [27]. When we attempted to replicate the study, analyzing the influence of refill consolidation and therapeutic complexity on nonadherence in Dutch data,

we were unable to identify a clinically meaningful predictor (Chapter 3.2). The latter finding confirms the findings of Steiner and Chan, that predictors from databases are not likely to be clinically relevant. This implicates that (1) readily available dispensing data might not be applicable to determine predictors of nonadherence and (2) that we should shift our focus to the predictive value of other less readily available patient related factors such as experiences with and beliefs about medication.

Predictors from patient beliefs about, and experiences with medicines

It is generally acknowledged that disease and treatment perceptions influence patients' adherence to therapy [28, 29]. Moreover, patients' health literacy and experiences could also influence adherence. Several questionnaires such as the Satisfaction with Information about Medicines Scale (SIMS) and the Beliefs about Medicines Questionnaire (BMQ) have been developed to measure this type of patient related factors which are not readily available in dispensing databases [30, 31]. Beliefs about medicines have been linked to both self-reported nonadherence and nonadherence based on dispensing data [30, 32]. A higher SIMS score was related to higher levels of reported adherence, indicating that a higher satisfaction with the information about medicines was related to better adherence [31]. The BMQ consists of two different questionnaires, the BMQg (general) and the BMQs (specific). The BMQs has a necessity and a concerns domain, which if subtracted yield a necessity-concerns differential. The necessity-concerns differential can be seen as a personal cost benefit analysis in which the patient weighs his concerns of taking medication against the perceived benefits. Research reported in this thesis (Chapter 4.1) investigated whether the BMQs is a static measure or if it changes during the course of therapy. We observed that compared with accepting patients, ambivalent patients had an almost 3 fold increased relative risk to become nonpersistent, the risk further increased to 5 for indifferent patients and to 6.6 for skeptical patients after one month of therapy. At the start of therapy a less pronounced and non-significant relative risk for nonpersistent patients was observed. This finding indicates that beliefs about medicines change during this initiation period (Chapter 4.1). If patient beliefs about their medicines change, it is possible that beliefs can be modified by healthcare workers. Changing patient beliefs may be a useful approach to investigate as an intervention to improve adherence.

Models to predict nonadherence

The possibility to discuss beliefs about medicines with every patient seen in the pharmacy or during appointments with a physician is limited, because time is lacking. It is therefore important to identify those patients that are at risk for nonadherence. A predictive model, with good positive predictive value (PPV) and/or a good negative predictive value (NPV), combined with reasonable sensitivity and specificity, would help health care providers [33-36]. This model should aid healthcare providers to elicit patients' beliefs about their medicines and should be easy to implement in daily (clinical) practice. Rating scales that identify nonadherence from self-reports do exist (e.g. the Medication Adherence Reporting Scale (MARS) and the Morisky scale), but do not predict (non)adherence at initiation of drug therapy [9, 37]. The model we provide in this thesis is easily administered to patients, has a high NPV (93%) with reasonable sensitivity and specificity and predicts (non)persistence during the initiation phase of drug therapy during which the patient's beliefs are more likely to be influenced by health care providers. Employment of this model in (clinical) practice should therefore be relatively easy.

The role of the pharmacist in nonadherence

Signal nonadherence

Unfortunately nonadherence can only be established retrospectively. When longitudinal dispensing data are available algorithms can calculate drug utilization and identify nonadherent patients. Pharmacists could invite patients suspected of nonadherence and discuss their beliefs and experiences with drug therapy. As it might be difficult to 'restore' adherence, it might be better to proactively motivate patients potentially at risk of nonadherence [38-41]. The studies presented in Chapters 4.1 and 4.2 suggest that patient attitudes towards medication at the start of therapy and early experiences with medication predict early discontinuation of therapy. This implies that pharmacists should proactively approach the patient in the early stage of therapy. During this initiation phase pharmacists should provide patients with information on drug therapy, but should also ask for patient beliefs and experiences. Both the necessity of treatment, worries and experiences of the patient and practical information should be discussed. Although it has not yet been proven whether such an approach will improve adherence, we will propose an intervention

based on the findings of this thesis. Future investigations are needed to show the value of such an intervention.

Interventions to improve adherence

Interventions that improve adherence are sparse and hardly effective [41]. However, many pharmaceutical care interventions have improved medication adherence have led to better intermediate outcomes such as blood pressure management, HbA1C and lipid levels and also to improved clinical outcomes in conditions such as asthma and heart failure [42, 43]. In a systematic review Cutrona et al. found that in-person pharmacist interventions were associated with a success rate of 83% [44]. Effective interventions however are mostly complex and therefore costly. There is an urgent need for simple but still effective interventions. A proactive approach focused on those patients at risk for nonadherence, during the initiation of therapy may be such a relatively simple and cheap intervention. Results from this thesis show that patient beliefs about chronic medication crystallize during the first month of therapy and that his behavior is predictable using a multivariate risk score (Chapter 4.1 and 4.2). From these results we infer that prevention is better than cure, so we propose a framework to prevent patients from becoming nonadherent. This framework exists of actions to be taken at the first, second and third prescription and at least one yearly face-to-face evaluation at a repeat prescription. In anticipation of changing beliefs during the first months of therapy, the framework has built in evaluation moments at 20-30 days and 90 days after the start of the new drug [45]. These evaluations are partly based on findings of this thesis and Dutch dispensing guidelines that state that a first drug should be dispensed for 2 weeks and repeat prescriptions are allowed for 3 months. In other health care settings we recommend similar evaluation moments relatively soon after the start of therapy and after a longer period [46, 47]. The first evaluation will focus on provision of information and the early beliefs of patients concerning their illness and medication, the second evaluation focuses on beliefs and experiences with medication, the third evaluation focuses on long-term experiences and the implementation of the use of medicines in patients daily routine.

At the start of a new prescription (t0) the pharmacist will provide information on drug therapy and will also ask the patient to fill in a short questionnaire after the initiation of drug therapy (i.e. after about one month). The pharmacist confirms contact details of the patient (e.g. telephone number and/or e-mail) and informs the patient that a short questionnaire will be mailed after 20-30 days (i.e. containing questions from BMQs and/or SIMS plus questions from

risk score model) as well as a proposed date for a discussion of the answers to the questionnaire and the experience with the new drug, for this is the period in which beliefs are most predictable for future nonpersistence (Chapters 4.1 and 4.2). After the questionnaires have been returned, the pharmacist assesses the patient's information needs and beliefs and risk for nonpersistence. Patients that do not return the questionnaire are contacted by telephone/e-mail, as we have shown that non-responders are more likely to become nonadherent (Chapter 4.3). At the appointment date, the pharmacist discusses any (drug related) problems or worries the patient brings up. Additional information will be provided if needed. At the end of the meeting, the pharmacist and the patient discuss whether it is feasible to adhere to the medication. In all patients the evaluation at 3 months will be aimed at issues that have arisen while the patient had to incorporate the drug regimen in his daily routines.
After this initiation phase has been completed, the pharmacist will regularly keep inviting the patient (e.g. yearly) to evaluate adherence and any (drug related) problems. Pharmacist will also calculate adherence from dispensing data and can use this to give feedback to the patient. The MARS questionnaire may reveal any uncertainties a patient may experience about his adherence, e.g. MPR may be as high as 98%, while the patient claims he misses an occasional dose. The MPR may be 50% and the patient reports never to have missed a dose. In the first example the reported adherence (i.e. MARS) may refer to a very adherent patient who seldom misses a dose, but feels like he is performing badly with respect to his drug taking compliance. Since MPR is very high, the pharmacist may reassure the patient. The second example may represent a wrong dosing entry in the pharmacies' database, because the patient reports never to miss a dose. Often dose changes are not actively changed in the pharmacies' database, while oral dose change instruction from a GP may have been given to the patient.

Cooperation between healthcare professionals

It is important to make improving adherence a joint effort of all healthcare providers including pharmacists, general practitioners (GP) and specialists. Once nonadherence has been signaled by one health care provider, it is necessary to stimulate patients to discuss specific problems or doubts about the necessity of treatment with other health care providers [48, 49]. In this field pharmacists can suggest important solutions, but cautiousness is needed as the pharmacist may miss important clinical information such as the indication for

drug treatment or laboratory values. It is therefore pivotal that all health care providers including pharmacists work together as a team and acknowledge each other's expertise [50-52]. Healthcare professionals should not supply the patient with conflicting messages, but their individual messages should reinforce each other and be tailored to the patient's specific situation [41].

Future challenges for pharmacists

Once a cooperative environment is established, pharmacists and physicians could explore even more innovative ways to further improve pharmacotherapy and adherence. Pre therapy counseling provided by the pharmacist could be an example of such an innovation [4,5,53-54]. In this pre therapy counseling a patient diagnosed with a chronic condition such as hypertension (unless this is a medical emergency) is referred to the pharmacist to discuss all drug treatment options. The pharmacist can discuss all pro's and con's of these therapies with the patient. Issues such as effectiveness, potential side effects, pill burden and drug interactions, as well as adherence to therapy could also be discussed. The pharmacist can supply the patient with the necessary information, which enables the patient to make an informed decision and confidently can start taking his medication. In a systematic review Cutrona et al. found that face-to-face contact with a pharmacist in a pharmacy were more effective (83% effectiveness) than in a clinic (38% effectiveness) [44]. This finding supports the implementation of face-to-face interventions in a pharmacy by a pharmacist. When the patient agrees the pharmacist can give feedback concerning patient beliefs and experiences to the patient's physician.

Studies in a wide range of chronic conditions have shown that the addition of a pharmacist to a health care team improves both adherence and intermediate clinical outcomes such as LDL, HbA1C and hypertension and clinical control of diseases such as asthma and heart failure [44, 51, 56-60]. These studies highlight the additional value of pharmaceutical care in chronic pharmacotherapy [61]. Moreover including pharmacists in the health care team may increase efficiency in the management of chronic therapies, because less time is needed for the physician to discuss pharmacotherapy with the patient and it optimizes the use of pharmacist's knowledge and improves shared decision making.

The influence of nonadherence on value in healthcare

How does patient compliance fit into the bigger picture of healthcare? Michael Porter has recently provided a framework on how to increase value in healthcare [62]. Porter defines value for patients as health outcomes achieved per dollar spent. Value could be considered as a ratio in which health outcomes are the numerator and cost the denominator. Increasing value unites the interests of both patients, health care providers and payers and is essential to maintain the economic sustainability of the health care system. Rewards for all actors in the health care system should be based on the creation of value and not on volume of services provided. Cost should not be based on individual services, but on the full cycle of care for every patient [62, 63]. In the proposed framework (Figure 1) towards health outcomes, adherence to medical treatment (including lifestyle and behavioral changes) plays an important role. As adherence is infrequently measured or taken into account when measuring health care outcomes, there is clearly a need for increase. Whereas high quality guidelines for the diagnosis and treatment of chronic conditions such as cardiovascular risk management, diabetes and depression exist and are updated continuously, adherence receives sparse attention in the development of protocols and guidelines. As guidelines should be based on scientific evidence this underlines the importance of studies into effective adherence improving interventions.

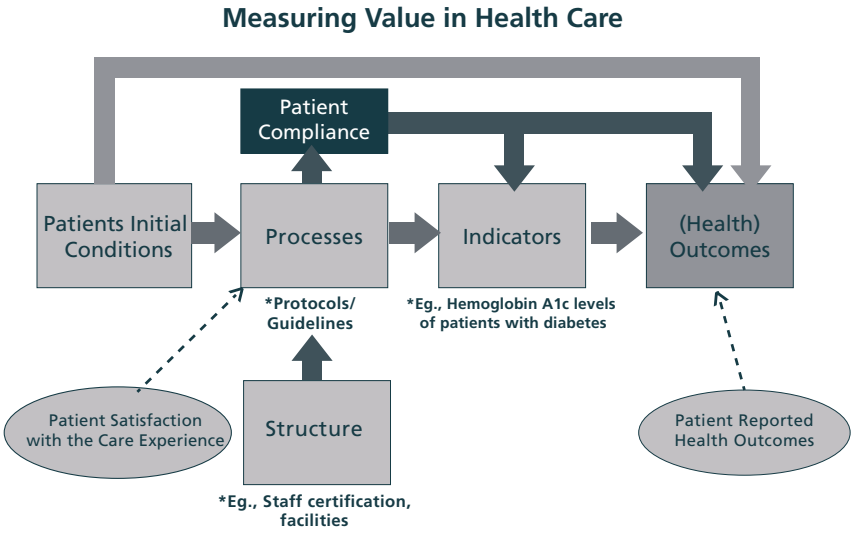

Figure 1: Overview of the factors that influence (health) outcomes according to Porter [62]

Table 1: Framework for the pharmacist to assist a patient at the initiation of drug therapy

Time (d)	Rx (number)	Actions
0	1	Give general information on drug treatment; explain most important practical details
		Make sure direct contact details such as email address or telephone number are known in the pharmacy
20–30	2–3	Give questionnaire to be filled in before appointment Contact nonresponders!
		Determine attitude and early experiences
		Discuss attitude, risk scores nonpersistence
		Discuss side effects and other possible drug related problems that may come up
90	3	Assess nonpersistence, if necessary take actions Discuss feasibility of incorporating dosing regimen in daily activitities
365		Evaluate adherence (e.g. MPR), validate with MARS or Morisky
		Discuss any (drug) related problems

Implications for future research / healthcare policy

The differences in the influence of therapeutic complexity on adherence between the US and The Netherlands suggests that healthcare systems can influence adherence. Whereas US health care providers call for more cohesion in pharmacy care, in The Netherlands and other European countries we see an increase in competition between healthcare providers especially pharmacies, which may lead to loss of the 'pharmacy home' and possibly more fragmentation of pharmacy care [26]. This could increase therapeutic complexity and as a consequence may increase nonadherence. The results from Chapter 3.2 indicate that currently no influence of therapeutic complexity exists in The Netherlands, but the study by Choudhry et al. suggest that fragmentation could lead to an increase of 8% in nonadherence [26]. If healthcare workers are to be rewarded on the basis of patient outcomes, medication adherence could be an important indicator [63]. If reimbursements are based on outcomes such as adherence, there should be sufficient incentive for all healthcare workers to jointly strive for such good (health) outcomes. All actors in the health care system should work efficiently and optimally use each other's expertise and knowledge.

Pharmacists can play an important role in both signaling and addressing poor medication compliance. They can provide the system with models to detect poor drug taking compliance or nonpersistence, may discuss issues related to the latter and may improve medication adherence (Chapter 4) [44, 51, 56-60]. Integrating pharmaceutical care in the care continuum for chronic patients optimally employs the expertise of pharmacists. This will increase the efficiency of the health care system and thus creates true value in healthcare.

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Summary

An increasing number of chronic conditions require long-term drug therapy. Medications do not work when you do not take them. Many people experience difficulties adhering to their medication. These difficulties are expressed in both complete discontinuation of medication and irregular intake of chronic medication. The omission of occasional doses while staying on therapy is described as poor drug taking compliance. Premature discontinuation of drug therapy is also called nonpersistence. Poor adherence can result in increased morbidity, mortality and avoidable health care costs. It is important to realize that nonpersistence and poor drug taking compliance have different reasons and motivations, both intentional and unintentional. Unfortunately poor adherence is generally detected retrospectively and it is difficult to predict future poor drug taking compliance or nonpersistence. The early identification of patients at risk for poor drug taking compliance or nonpersistence would aid physicians and pharmacists to focus their counseling on patients at risk of erratic drug taking. This thesis focuses on the influence of measurement methods and definitions of adherence on reported outcomes of nonperistence and poor drug taking compliance (Chapter 2). Secondly it focuses on prediction of poor drug taking compliance and nonpersistence from both historical dispensing data and patient beliefs (Chapters 3 and 4).

Measuring adherence

In Chapter 2.1 the effects of discrimination between the reporting of either poor drug taking compliance, nonpersistence or both on estimated adherence of statins is investigated. If studies reported both poor taking compliance and nonpersistence, drug taking compliance was 14% better and nonpersistence 19% lower compared to studies reporting only poor drug taking compliance or only nonpersistence. This underlines the importance of differentiating between poor drug taking compliance and nonpersistence in the reporting of study outcomes on adherence. Studies that identified nonpersistence through self-report reported 19% lower nonpersistence rates compared to studies using computerized dispensing records. Patients using statins for primary prevention of cardiovascular disease showed 16% poorer drug taking compliance compared to patients taking a statin after a myocardial infarction or other cardiovascular event (secondary prevention). New users more frequently discontinued statin therapy compared to prior statin users. Increasing the length of time without statins before patients were classified as being nonpersistent, decreased the percentage of nonpersistent users.

The influence of different methods of calculating the exposure to statins on the outcome nonpersistence was further investigated in Chapter 2.2. Exposure to statins was calculated with and without taking previous supplies into account. Nonpersistence was 7% lower if supplies from previous dispensings were taken into account, but this difference disappeared at gap lengths of 90 days or longer.

Predicting adherence from historical dispensing data

Prediction of long-term poor drug taking compliance from early poor drug taking compliance was investigated in Chapter 3.1. Age <60 years, <30 prescriptions in the preceding year, <20 different drugs between inclusion and index date and poor drug taking compliance at the third fill predicted poor long-term drug taking compliance. These variables were combined in a multivariate model and each variable was assigned a risk score, which, if combined, added up to a total risk score. A risk score higher than the proposed cutoff value identified patients at risk for long-term poor drug taking compliance. The efficiency increased from 16% to 35% when using the prediction model. This translates in 5 patients needed to screen to identify one patient at risk of long-term poor drug taking compliance.

The influence of therapeutic complexity on nonpersistence with statins was investigated in Chapter 3.2. From the PHARMO database 6,614 new statin users were identified. The number of pharmacy visits, number of single drug dispensings (e.g antibiotics or corticosteroid courses), number of different prescribers, and the number of changes within each drug class predicted nonpersistence with statins. Odds ratios however were very close to one, indicating that the predictive value of these variables was limited. Comparable research in the US however found that therapeutic complexity was associated with an 8% increase of poor drug taking compliance. The creation of a 'Pharmacy Home' or a single pharmacy and dispensing of larger quantities per pharmacy visit are important recommendations made in the US study. In The Netherlands these recommendations are almost completely implemented already. This indicates that differences in health care systems influence adherence more strongly than therapeutic complexity.

Predicting adherence from patient beliefs

Patient beliefs can be measured using the beliefs about medicines questionnaire (BMQ). Two versions of the BMQ exist. The BMQ-general (BMQg) measures beliefs about medication in general. The BMQ-specific (BMQs) measures beliefs about a specific drug used by a patient. The satisfaction of information about medicines scale (SIMS) measures the degree of satisfaction a patient has about the information that was provided about the prescribed drug. In Chapter 4.1 the BMQs is used to measure if beliefs about medication are stable or whether they change over time. The BMQs consists of a necessity and concerns domain, which are covered by five questions each. From the necessity and concerns scores, four different attitudes can be defined, accepting (high necessity, low concerns), ambivalent (high necessity, high concerns), indifferent (low necessity, low concerns) and skeptical (low necessity, high concerns). Expected is that accepting patients discontinue treatment less often than skeptical patients. Results described in Chapter 4.1 indicate that at the start of therapy, beliefs do not strongly predict nonpersistence, but after one month they do. It was found that patients who were skeptical after one month had a 6.6-increased risk to discontinue treatment within 10 months compared to accepting patients. It appears that beliefs about medication change during the early course of therapy. This implicates that physicians and pharmacists should address beliefs early after the start of therapy and discuss them with patients.

Prediction of nonpersistence from patient beliefs is investigated in Chapter 4.2, using the BMQg, BMQs and SIMS. After one month a predictive model for nonpersistence could be constructed. Three individual questions appeared to predict nonpersistence: (1) 'People who take medicines should stop their treatment for a while now and then', (2) 'Have you received information about what you should do if you experience unwanted effects' and (3) 'This medicine has unpleasant side effects'. Sensitivity of the model was 86% and specificity 66% at the proposed cutoff value. Sensitivity is the chance of predicting future nonpersistence, specificity is the chance of ruling out future nonpersistence. The positive predictive value (PPV) is the relative frequency of the model being correct was 44% and the negative predictive value (NPV) or the relative frequency of not becoming nonpersistent if the model predicts so was 93%. Due to the high NPV, it is possible to discriminate between patients at risk for nonpersistence and patients not at risk for nonpersistence, which makes the model attractive for clinical practice.

Non-response to a questionnaire and the association with nonpersistence were investigated in Chapter 4.3. In patients who received a questionnaire within one week after a drug for chronic use was dispensed, the response rate was 50%. Of the responders 33% were nonpersistent and of the non-responders this was 55%. Non-response was associated with an increased risk for nonpersistence of 1.9. Researchers, pharmacists and physicians to identify potential nonpersistent patients could use this finding.

General discussion

In Chapter 5 the main findings of this thesis are discussed in a broader perspective. First, recommendations for measuring adherence are made. Differentiating between drug taking compliance and nonpersistence should standardize adherence reports. In addition the way adherence has been measured leads to different adherence estimates. Furthermore definitions as well as cutoff values influence adherence outcomes. We propose, when using databases to estimate drug taking compliance, that the medication possession ratio (MPR) and the proportion of days covered (PDC) should be used, because the latter two methods are used in the majority of studies. Cutoff values should include long enough gaps to differentiate between persistent and nonpersistent patients. If short gaps are used, researchers should account for supplies from earlier dispensings. When measuring drug taking compliance, cutoff values that make sense should be chosen instead of the arbitrarily cutoff value of 80% that is mostly used in the literature. 'Forgiveness' of the drug as well as risks associated with poor drug taking compliance (e.g. development of viral resistance in patient with poor anti-retroviral drug taking compliance) should determine the most logical cutoff value.

Historical dispensing data do not predict adherence very well, although therapeutic complexity may play a modest role. Especially fragmentation of pharmaceutical care and refill consolidation were associated with this decrease in adherence. Policymakers in The Netherlands should therefore focus on prevention of fragmentation of pharmaceutical care. Medication beliefs should be discussed with the patient during the early course of therapy. A predictive model is proposed that provides pharmacists and physicians with a tool to identify patients at risk for nonpersistence.

A framework for the detection and improvement of nonadherence by pharmacists is presented. The proposed framework uses a proactive approach in which beliefs about medicines (Chapter 4.1) play a central role. Cooperation between healthcare providers is strongly emphasized. In the last part of the

general discussion the importance of adherence in the improvement of 'value in healthcare' is addressed. It appears that poor adherence is a very important factor that has negative impact on patient outcomes and thus decreases value in healthcare. It is recommended that adherence and improvement of adherence is incorporated in guidelines and it is important to stress the importance of the way adherence should be promoted in patients and to make this a joint task of all healthcare providers. Improvement of adherence will improve the efficiency of the healthcare system and thus will create true 'value in healthcare'.

Chapter 5.3

Samenvatting

Veel aandoeningen worden langdurig behandeld met medicatie. Het is daarbij belangrijk dat de voorgeschreven medicatie goed gebruikt wordt. Veel mensen gebruiken hun medicatie echter niet op de voorgeschreven wijze. Het niet gebruiken van medicatie volgens voorschrift wordt ook wel slechte therapietrouw of therapieontrouw genoemd. Er zijn twee vormen van therapieontrouw te onderscheiden. De eerste is het stoppen (persistentie) met medicatie en de tweede gaat meer over de kwaliteit van het innemen van medicatie. In dit laatste geval blijft de gebruiker het geneesmiddel wel doorgebruiken, maar neemt het bewust of onbewust niet elke dag in, zoals wordt voorgeschreven. Therapieontrouw kan ertoe leiden dat een aandoening minder goed onder controle is en soms zelfs tot onnodige ziekenhuisopnamen. Daardoor worden de kosten van de gezondheidszorg onnodig verhoogd. Belangrijk is ook dat men zich realiseert dat de onderliggende processen voor het stoppen met medicatie en het overslaan van doseringen waarschijnlijk een verschillende oorzaak hebben en dat er verschillende motivaties zijn voor deze twee vormen van gedrag. Helaas kan therapieontrouw pas achteraf worden vastgesteld; er is geen manier om mensen die een nieuw geneesmiddel minder goed zullen gaan innemen voorafgaand aan het gebruik te herkennen. Het herkennen van mensen met een verhoogde kans op therapieontrouw zou artsen en apothekers kunnen helpen om deze mensen beter te begeleiden bij het geneesmiddelgebruik. In dit proefschrift wordt therapietrouw op twee verschillende manieren benaderd, als eerste wordt er gekeken hoe verschillen in meetmethoden van therapietrouw de uitkomst beïnvloeden (Hoofdstuk 2). Als tweede wordt gekeken of therapieontrouw kan worden voorspeld uit gegevens uit het verleden (Hoofdstuk 3) en uit opvattingen die mensen hebben over hun medicatie (Hoofdstuk 4).

Het meten van therapietrouw

In Hoofdstuk 2.1 wordt gekeken of het maken van een onderscheid tussen het helemaal stoppen en een slechte kwaliteit van inname van cholesterolverlagers (zogenaamde statines) de mate waarin er therapieontrouw wordt geconstateerd, beïnvloed. Het blijkt dat veel onderzoeken geen onderscheid maken tussen deze twee vormen van therapieontrouw en alles bij wijze van spreken op een hoop gooien. Het blijkt dat in onderzoeken waar dit onderscheid wel wordt gemaakt een lager percentage stoppers en een lager percentage slechte innemers wordt gevonden. Deze verschillen bedroegen 19% en 14% respectievelijk.

Verder bleek dat onderzoeken waarin het stoppen werd vastgesteld op basis van zelfrapportage door de gebruikers 19% minder stoppers vonden dan wanneer het stoppen werd vastgesteld op basis van computerbestanden van artsen, apothekers of verzekeraars. De variatie in uitkomsten van het niet goed innemen van statines kon verder worden verklaard door de reden van gebruik. Mensen die statines gebruikten ter preventie van de ontwikkeling van hart- en vaatziekten (primaire preventie) bleken deze slechter in te nemen dan mensen die statines gebruikten bij een aanwezige hart- en/of vaatziekte, zoals een doorgemaakt hart- of herseninfarct.Verder bleken nieuwe gebruikers frequenter te stoppen dan langdurige gebruikers en bleek dat als de periode waarbij geen medicatie beschikbaar was om in te nemen toenam, het percentage stoppers afnam. Tenslotte lieten studies die gesponsord werden door de farmaceutische industrie een slechtere inname zien van statines dan studies die niet gesponsord werden of waarbij dit onbekend was. Deze observatie is te verklaren uit het feit dat studies die door de farmaceutische industrie gesponsord werden, therapietrouw meestal rapporteerden als het slecht innemen van medicatie in plaats van ook het stoppen van medicatie te rapporteren en dat sponsoring dus eigenlijk niet de werkelijke oorzaak is van het gevonden verschil.
In Hoofdstuk 2.2 onderzochten wij of de manier waarop de blootstelling aan statines werd gemeten en de manier waarop het stoppen met statines werd gemeten van invloed was op de uitkomst 'stoppen'. De blootstelling aan statines werd bepaald op twee manieren. In de eerste manier werd er vanuit gegaan dat mensen alle voorraden die theoretisch nog in huis waren, gebruiken totdat er geen statine meer beschikbaar is om in te nemen. Bij de tweede manier werd alleen gekeken naar de tijd tussen twee afhaaldata in de apotheek en werd geen rekening gehouden met eventuele opgebouwde voorraden. Het bleek dat als er rekening gehouden wordt met voorraden die zijn opgebouwd uit vroegere verstrekkingen door de apotheek, ongeveer 7% minder mensen worden geclassificeerd als stopper. Dit verschil bleek langzaam minder te worden als de minimale periode waarin theoretisch geen statine meer aanwezig was voordat iemand als stopper werd geclassificeerd, langer werd gemaakt. Bij een periode van 90 dagen of langer zonder beschikbaarheid van een statine bleek er geen verschil meer te zijn tussen het feit of er wel of geen rekening gehouden werd met voorraden uit het verleden.

Het voorspellen van therapietrouw uit apotheek-aflevergegevens

In Hoofdstuk 3.1 werd onderzocht of bepaalde factoren gemeten tijdens de eerste vijf afleveringen van een nieuw geneesmiddel de therapietrouw op de langere termijn kunnen voorspellen. Het bleek dat leeftijd < 60 jaar, het aantal voorschriften <30 en het aantal verschillende geneesmiddelen <20 en een slechte kwaliteit van de inname van het geneesmiddel in de eerste periode van gebruik (aantal dagdoses/observatie periode) <0.80 voorspellend waren voor slechte kwaliteit van inname op de lange termijn. Deze individuele variabelen zijn samengevoegd tot een model, waarbij aan elke variabele een risicoscore werd toegekend. Het optellen van de individuele risicoscores leidde tot een totale risicoscore. Indien deze risicoscore groter was dan het voorgestelde afkappunt, nam de efficiëntie om mensen met een slechte kwaliteit van inname van hun medicatie te identificeren toe van 16% naar 35%. Het aantal mensen dat gescreend zou moeten worden om 1 persoon met een lange termijn slechte kwaliteit van inname te identificeren (Number Needed to Screen) bedroeg 5.
De invloed van complexiteit van de totale behandeling met geneesmiddelen op het stoppen met medicatie en een slechte kwaliteit van inname werd onderzocht in Hoofdstuk 3.2. Uit de PHARMO database werden 6.614 nieuwe gebruikers van statinen geselecteerd. Het bleek dat het aantal: apotheek bezoeken, afleveringen, eenmalige afleveringen (bijvoorbeeld antibiotica, of prednisolon stootkuren), verschillende voorschrijvers en wisselingen binnen een geneesmiddelen groep (van statine 1 naar statine 2 of van antidepressivum 1 naar antidepressivum 2) voorspellend waren voor het staken met geneesmiddelen. Een slechte kwaliteit van inname bleek alleen voorspeld te worden door het aantal eenmalige afleveringen. Hoewel de voorspellende variabelen allemaal statistisch significant waren, bleek dat de voorspellende waarde minimaal was, omdat de odds ratios (benadering van het relatieve risico) allemaal dicht bij 1 lagen. In tegenstelling tot wat collega onderzoekers in de VS vonden, bleek in de Nederlandse situatie de complexiteit van aflevergegevens geen belangrijk verband te hebben met een verminderde therapietrouw. Een aantekening die gemaakt moet worden is dat in Nederland in tegenstelling tot de VS patiënten in de meeste gevallen slechts 1 apotheek hebben waar alle medicatie wordt afgehaald. In de VS zijn dat er meestal veel meer. Een van de aanbevelingen van de Amerikaanse studie was het instellen van een 'Pharmacy Home' ofwel een vaste apotheek voor iedere patiënt. In de Nederlandse situatie is aan

deze voorwaarde voldaan en dus lijkt het dat het systeem van de gezondheidszorg een belangrijke invloed kan hebben op therapietrouw.

Opvattingen over medicatie en therapietrouw

De opvattingen die mensen hebben over hun medicatie kunnen gemeten worden met de Beliefs about Medicines Questionnaire (BMQ). De BMQ bestaat uit twee verschillende versies, de BMQ-general (BMQg) meet de opvattingen over medicatie in het algemeen en de BMQ-specific (BMQs) over het specifieke geneesmiddel dat is voorgeschreven. Verder bestaat er de Satisfaction of Information about Medicines Scale (SIMS) die meet in hoeverre men tevreden is over de informatie die men heeft ontvangen over het voorgeschreven medicijn.
In Hoofdstuk 4.1 wordt onderzocht of de opvattingen over medicatie stabiel zijn of niet. De BMQs bestaat uit vijf vragen over zorgen die mensen hebben over hun medicatie en vijf vragen over de noodzaak van hun medicatie. Uit de BMQs zijn vier verschillende houdingen over medicatie geclassificeerd. Mensen met veel zorgen en lage noodzaak worden geclassificeerd als sceptisch, mensen met lage noodzaak en weinig zorgen als onverschillig, hoge noodzaak en veel zorgen als ambivalent en hoge noodzaak en weinig zorgen als accepterend. De verwachting is dat mensen die een accepterende houding ten opzichte van hun medicatie hebben, minder snel stoppen dan mensen met een sceptische houding. Uit het onderzoek beschreven in Hoofdstuk 4.1 blijkt dat bij start van de therapie er weinig gezegd kan worden over de houding van mensen en het staken met hun medicatie. Na 1 maand echter bleek dat mensen die weinig noodzaak inzien van het gebruik van hun medicatie een verhoogde kans hebben om te stoppen. Deze kans was nog eens verhoogd als mensen ook nog veel zorgen over hun medicatie hadden (relatief risico op stoppen was 6.6 vergeleken met mensen die een accepterende houding hadden). Het lijkt er dus op dat opvattingen over medicatie veranderen aan het begin van de therapie en dat dit ook de periode is waarin zorgverleners moeite zouden moeten steken om de opvattingen van mensen te bespreken om wellicht de toekomstige therapietrouw te verbeteren.
In Hoofdstuk 4.2 wordt met behulp van de BMQg, BMQs en de SIMS onderzocht of er een voorspellend model gemaakt kan worden voor stoppen met medicatie. Het bleek dat zowel aan het begin als na 1 maand een voorspellend model gemaakt kon worden, maar dat het model dat na 1 maand geconstrueerd werd betere voorspellende eigenschappen bezat. Drie vragen bleken voorspellend, namelijk (1) ‘Mensen die medicatie gebruiken zouden deze zo nu en dan hun behandeling moeten stoppen’, (2) ‘Heeft u voldoende

informatie ontvangen over wat u moet doen als u ongewenste bijwerkingen ervaart' en (3) 'Dit geneesmiddel heeft onplezierige bijwerkingen'. Het model had een sensitiviteit van 83% en een specificiteit van 66% bij het voorgestelde afkappunt. Sensitiviteit van een model geeft aan in hoeverre het model stoppen met medicatie juist voorspelt en specificiteit geeft aan in hoeverre het model voorspelt dat iemand niet stopt als dat ook daadwerkelijk het geval is. De positief voorspellende waarde (PPV), ofwel de relatieve frequentie dat het model de waarheid voorspelt was 44% en de negatief voorspellende waarde (NPV) was 93%. De negatief voorspellende waarde geeft aan welk percentage van de mensen inderdaad niet staakt met de medicatie wanneer het model voorspelt dat zij zullen doorgaan. Met name de NPV is hoog, dat betekent dat iemand met een risicoscore onder het afkappunt 93% van de gevallen ook niet stopt met zijn medicatie. Met dit model kan dus goed onderscheid gemaakt worden tussen mensen die een risico lopen om te stoppen en mensen die dit niet doen. Het model kan daarom goed worden toegepast in de dagelijkse praktijk.
In Hoofdstuk 4.3 werd onderzocht of niet reageren een verhoogde kans gaf op staken met medicatie. Van alle mensen die in eerste instantie een enquête toegezonden hadden gekregen reageerde 50%. Het bleek dat van de mensen die reageerden 33% hun medicatie staakten op enig moment. Bij de mensen die niet reageerden bedroeg dit percentage 55. Het niet reageren op een enquête was geassocieerd met een verhoogd risico van 1,9 op het staken met de medicatie. Onderzoekers, maar ook apothekers en (huis)artsen moeten dus rekening houden met mensen die niet reageren op vragenlijsten en moeten daar extra aandacht aan besteden als ze geïnteresseerd zijn in de therapietrouw van deze mensen. Het bleek verder uit dit onderzoek dat de snelheid van terugsturen van de enquête geen invloed had op het wel of niet voortijdig staken met medicatie.

Algemene discussie over de bevindingen uit dit proefschrift

In Hoofdstuk 5 worden de bevindingen uit dit proefschrift in een breder perspectief geplaatst. Allereerst worden aanbevelingen gedaan over de manier van meten van therapietrouw. Therapietrouw moet op een gestandaardiseerde manier gerapporteerd worden, namelijk door zowel het staken van, als de kwaliteit van inname van het geneesmiddel te rapporteren. Zowel the International Society for Pharmacoeconomics and Outcome Research (ISPOR) als the Ascertain Barriers for Compliance (ABC) project concluderen dit onafhankelijk van elkaar en dit blijkt ook uit de resultaten van Hoofdstuk 2.1. Verder dient er rekening gehouden te worden met de manier waarop therapietrouw gemeten is. Zelfrapportage geeft andere resultaten dan als er een database gebruikt

wordt gebaseerd op apotheek aflevergegevens. Definities en afkapwaarden beïnvloeden de gerapporteerde therapietrouw uitkomsten zoals is beschreven in Hoofdstuk 2.2. Wij adviseren om in databases gebruik te maken van de MPR (medication possession ratio) en de PDC (proportion of days covered), omdat deze twee methodes verreweg het meest gebruikt worden in studies die de kwaliteit van inname van de medicatie bestuderen. Het wordt door beide methodes te gebruiken makkelijker om studies met elkaar te vergelijken en conclusies te trekken. De afkapwaarden die gebruikt worden om stoppen met medicatie te kwantificeren dienen voldoende lang gekozen te worden, zodat ook daadwerkelijk wordt gekeken naar klinisch relevante gevallen. Verder moet er rekening gehouden worden met voorraden uit eerdere afleveringen indien een korte periode zonder medicatie relevant wordt geacht in de bewuste studie. Bij het meten van de kwaliteit van inname van de medicatie moet het afkappunt zo gekozen worden dat rekening gehouden wordt met de 'forgiveness' van het geneesmiddel. In de praktijk wordt vaak gekozen voor aan afkappunt van 80%, terwijl dit voor bijvoorbeeld antivirale middelen tegen HIV infectie veel hoger moet liggen dan bijvoorbeeld acetylsalicylzuur. Het onderzoek naar 'forgiveness' staat nog in de kinderschoenen en is een belangrijk gebied om verder onderzoek naar te doen.

Het voorspellen van therapieontrouw (slechte kwaliteit van inname en stoppen met medicatie) is een belangrijk onderwerp omdat therapieontrouw veelal achteraf wordt vastgesteld. Het lijkt erop dat (Hoofdstuk 3) resultaten uit het verleden geen garantie bieden voor de toekomst, hoewel complexiteit rondom het verkrijgen van geneesmiddelen een beperkte rol lijkt te spelen. Nederland doet er daarom goed aan om ervoor te zorgen dat de farmaceutische zorg niet te veel versnipperd raakt. Een grote studie in de VS heeft laten zien dat dit gepaard kan gaan met een afname in therapietrouw van 8%. Verder is het belangrijk dat opvattingen van patiënten over hun geneesmiddelen een belangrijkere rol gaan spelen in de gezondheidszorg en met name in de apotheek. Apothekers zouden de opvattingen van patiënten samen met hen moeten bespreken en bediscussiëren, dit kan het beste gebeuren in de periode na de start van een nieuw geneesmiddel. Het voorspellende model dat is beschreven in Hoofdstuk 4.2 lijkt een aantrekkelijk model om toe te passen in de dagelijkse praktijk, maar validatie in een vergelijkbare populatie wordt aanbevolen.

De apotheker heeft een rol in het signaleren van therapieontrouw en in het implementeren van een therapietrouw verbeter traject in de apotheek. In de algemene discussie wordt een mogelijk traject voorgesteld, gebaseerd op de

resultaten van het onderzoek uit dit proefschrift. Het voorgestelde traject gaat uit van een proactieve aanpak, waarbij het voorspellende model uit Hoofdstuk 4.2 en de opvattingen over geneesmiddelen centraal staan. Er wordt geadviseerd dat alle werkers in de gezondheidszorg die met therapietrouw te maken hebben samenwerken en een consistente boodschap verkondigen aan de patiënt. Een mogelijk toekomst scenario voor de apotheker wordt geschetst, namelijk het pre therapeutisch consult. Hierin kan de apotheker voordat de patiënt begint met zijn geneesmiddel samen met hem of haar een afweging maken welk middel het beste is en hierover feedback geven aan de voorschrijvend arts. Een dergelijke aanpak zou moeten leiden tot een situatie waarbij de patiënt veel meer betrokken is bij zijn of haar eigen farmacotherapie. Nu is onderzocht welke personen een verhoogd risico lopen op therapieontrouw en deze personen geïdentificeerd kunnen worden, is het van belang te weten welke interventie het beste kan worden gedaan om te zorgen dat mensen hun geneesmiddelen blijven gebruiken en ook op de juiste manier blijven gebruiken. Deze laatste vraag blijft tot op heden nog onbeantwoord.

Ten slotte wordt er ingegaan op de rol van therapietrouw bij het bereiken van 'meerwaarde in de gezondheidszorg', Het lijkt erop dat therapie(on)trouw een belangrijke factor is die uitkomsten in de gezondheidszorg beïnvloed. Het advies om therapietrouw als variabele mee te nemen in allerlei richtlijnen die gemaakt worden is een belangrijk aandachtspunt. Het is ook belangrijk om afspraken te maken over de uitvoering hiervan en deze in te bedden in de richtlijnen om de efficiency van onze gezondheidszorg te verbeteren en die 'meerwaarde' ook echt te creëren.

Chapter 5.4

Dankwoord

Het doen van promotieonderzoek, heb ik ondervonden, is geen eitje. Ooit begon ik met het idee 'dat doen we er wel even bij', maar van dat idee ben ik teruggekomen. Allereerst moet je heel kritisch blijven en zelfs als je denkt dat je kritisch bent, dan ben je niet kritisch genoeg. Je moet zelfstandig zijn en vooral nooit opgeven. De beloning die je krijgt als het dan lukt is zeer bevredigend. Tijdens mijn onderzoek heb ik enorm veel geleerd, veelal door zelfstudie en ook vaak met hulp van anderen. Deze ervaring had ik nooit kunnen ondergaan als een aantal personen er niet was geweest. Ik ben heb dan ook zeer dankbaar voor de bijdrage(n) die ze hebben geleverd.

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Chapter 5.5

About the author

Harm Geers was born on February 23, 1970 in Bennekom, The Netherlands. After finishing secondary school (VWO), the Marnix College in Ede, he started his pharmacy study at Rijksuniversiteit Groningen in 1988. During his study he was president of 'Pharmaciae Sacrum', the pharmacy student association of the school of Pharmacy in Groningen from 1991-1992. His first research experience was at the Harvey W. Peters Research Center for the study of Parkinson's disease and disorders of the central nervous system at Virginia Tech where he studied medicinal chemistry under professor Neal Castagnoli Jr. in 1993. After obtaining his master's degree, he started his training as a pharmacist, which he finished in 1995. Being the last pharmacist who was drafted by the Dutch army he was stationed at the Central Military Hospital in Utrecht the Netherlands in 1995 and after a year of military experience in the Dutch army he started his career as a community pharmacist in 1996. During his spare time on Monday mornings Harm started his PhD research in 2003, which eventually appeared not to be an effective schedule. After working one day a week from 2005 and increasing it to two days in 2007 the process was speeded up and led to this final result. Besides his work as a pharmacist, Harm is also working on integrating health care for elderly patients in Bennekom as well as working on an intervention to improve adherence, based on this thesis. The first project was rewarded a grant of € 85,000 by ZonMw and is currently implemented in Bennekom. The second project was selected by health insurer Achmea for a grant to stimulate innovation in pharmacies. In the future Harm would like to stay devoted to improve the position of pharmacists in The Netherlands, be involved in pharmacoepidemiologic research and to be able to contribute to the improvement of the Dutch health care system by improving integration of care and cooperation between health care workers.